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Bioabsorbable implants in paediatric supracondylar fractures of the elbow

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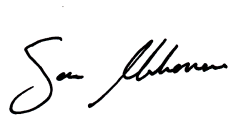
Declaration

This thesis and its composition are entirely my own work. The contributions and assistance of others in data analysis have been appropriately acknowledged. The research described has been carried out by me, under the supervision of Mr Tim White and Mr Alastair Murray. I have not submitted this work in candidature for any other degree or diploma of professional qualification.



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This thesis is dedicated to my family. Their unconditional love and support is everything to me.

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Thesis Abstract

Background. Operative stabilisation of paediatric supracondylar elbow fractures is most commonly achieved through the use of percutaneous Kirschner wires. These implants are inert, cheap and simple to use. However, the requirement for removal and the possibility of pin site infection provides opportunity for the development of new techniques that eliminate these drawbacks. Bioabsorbable pins that remain *in situ* and allow definitive closure of skin at the time of surgery could provide such advantages. However, their ability to maintain fracture reduction and their effect on the growth plate has not been adequately evaluated.

Hypotheses. The Acumed® Biotrak Helical Nail (a bioabsorbable fixation implant) has comparable strength to Kirschner wires and does not result in significant disruption of the growth plate or subsequent growth.

Studies. Three complementary studies were performed. (1) A retrospective cohort analysis was performed to establish the prevalence of complications related to Kirschner wire fixation of paediatric supracondylar elbow fractures. (2) A saw-bone model was designed to compare the mechanical performance of the Helical Nail and Kirschner wires. (3) An ovine model was designed to assess the *in vivo* effects of the Helical Nail on limb growth and physeal morphology. The surgical practicalities of the device and its potential for use in the paediatric setting were evaluated. The primary outcome was femoral length six months after Helical Nail insertion. Micro-CT evaluation of growth plate thickness, percentage disruption and bony infiltration was undertaken – the first time this technique has been used in a large animal study. Traditional histopathological techniques complimented the Micro-CT analysis and offered comment on the microscopic appearance of the growth plate immediately adjacent to the bioabsorbable nails.

Results. The infection rate within a large tertiary referral centre was 9.6%, which was marginally higher than previous cohort studies. Mechanical testing demonstrated that the Helical Nail had comparable strength in rotation, but inferior resistance to posterior translation, when compared to Kirschner wires. In the ovine model, the Helical Nail disrupted 3.4% of the physis. The nails had no effect on femoral growth during the six month study period. Micro-CT analysis of both the helical nail and Kirschner wire groups demonstrated multiple bony bridges, with two cases of physeal tethering in the Helical Nail group. There was no difference in physeal thickness or bony infiltration of the physis. Histopathology did not reveal any significant inflammatory or foreign body reaction adjacent to the nails.

Conclusion. The Helical Nail demonstrated a number of encouraging attributes which indicate its potential. However, in its current state the device is not suitable for use in the stabilisation of paediatric supracondylar elbow fractures.

Lay Summary

Fractures in children often occur near the growth plate; a specialised region responsible for forming new bone. Certain fractures, such as those located above the elbow joint, require fixation with wires that traverse the growth plate in order to achieve adequate stability. The eponymously named Kirschner wire is the most common method of fixation and has an established record of success without undue damage to the growth plate. The wires cannot be left inside the bone indefinitely so are left protruding from the skin to facilitate their removal. These wires have two main drawbacks (1) the protruding wires ends can be a cause of infection and (2) children find removal unpleasant. A solution would be the use of a dissolvable pin that would be left inside the bone indefinitely, which would limit risk of infection and eliminate the need for removal procedures.

This study evaluated a bioabsorbable pin, the Biotrak Helical Nail, and its suitability of the stabilisation of elbow fractures in children. Firstly, the mechanical characteristics of the Helical Nail were compared to the established standard of Kirschner wires. Secondly, the effects of the Helical Nail on the growth plate of sheep and whether the nails hindered growth, were defined. Specialist ultra-high resolution computerised tomography (CT) scans were used for the first time in this setting.

This study demonstrated that while the Helical Nail neither hindered growth, nor caused abnormal appearances of the growth plate of sheep, it had inferior mechanical characteristics. In its current form, the Helical Nail is not suitable for human use, although there are clear avenues for development.

Section 1: Introduction

1.1 THE CLINICAL PROBLEM

Paediatric supracondylar elbow fractures are commonly stabilised by the insertion of trans-physeal steel pins, eponymously named Kirschner wires. The implants are inert, cheap to manufacture and provide adequate fixation. They are most commonly employed in a percutaneous fashion with the ends left protruding from the skin to facilitate subsequent removal. There are two main drawbacks to this fixation method, (1) the protruding wires offer a portal for infection and (2) their requirement for removal. Infection is the greatest concern, with the potential for significant morbidity in cases of deep soft tissue spread or osteomyelitis. Bioabsorbable pins might offer a solution to both issues: implants that can be inserted with primary skin closure at the time of surgery, and no need for removal. Any bioabsorbable device with the potential to supplant Kirschner wires must demonstrate comparable strength without causing clinically significant damage to the growth plate or subsequent limb development.

1.2 GROWTH PLATE INJURIES

1.2.1 Growth plate physiology

The growth plate, or physis, is the essential structure that provides longitudinal growth during skeletal development. The physes lie between primary and secondary ossification centres and form bone via endochondral ossification, the process of bone formation via a cartilaginous matrix. The physis has numerous zones that follow the transition of chondrocytes to ossified bone (Figure 1.1).

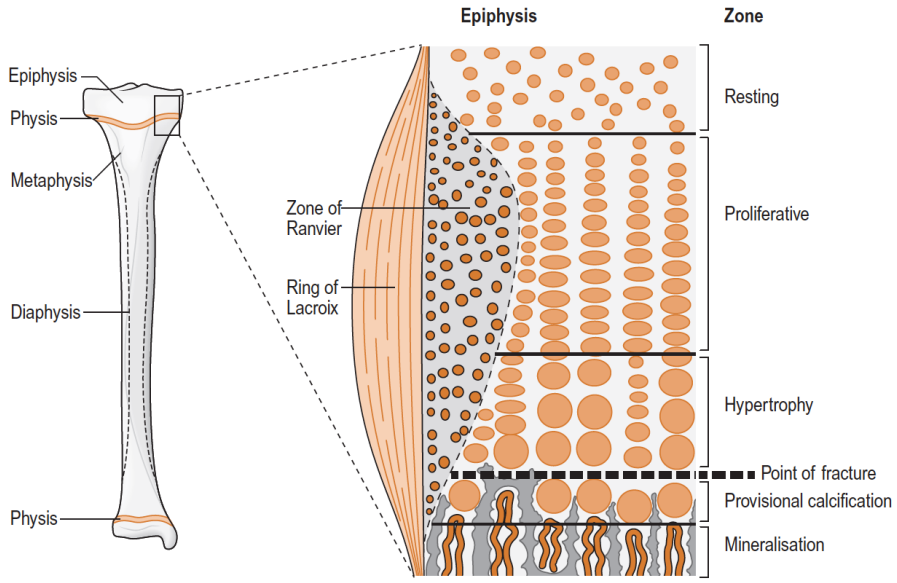

Figure 1.1: The growth plate. With permission from the authors of "McRae's Orthopaedic Trauma and Emergency Fracture Management".

- **The resting zone**. Also referred to as the reserve zone, consists of small, sparse and irregularly arranged groups of spherical stem cells that are responsible for generating the chondrocytes of growth.
- **The proliferative zone**. The chondrocytes undergo mitosis, becoming more numerous before arranging into columns running parallel to the axis of growth.

- **The zone of hypertrophy**: The cells increase to 4-5 times their previous volume, while matrix vesicles are deposited within the longitudinal septa of the physis.
- **The zone of provisional calcification/mineralisation.** Also referred to as the zone of endochondral ossification, chondrocytes undergo apoptosis with the invasion of blood vessels from the metaphysis, and impregnation of calcium salts into the extracellular chondroid matrix (1).

The periphery of the physis has specialised regions. The zone of Ranvier is a triangular structure that resides on the boundary of the physis containing fibroblasts, chondrocytes and osteoblasts and is responsible for the peripheral growth of the physis. It is complimented by the perichondral ring of LaCroix, a fibrous structure overlying the zone of Ranvier, connecting the metaphyseal periosteum and the cartilaginous epiphysis, thus stabilising the epiphysis to the metaphysis.

Growth plate maturation and closure

Longitudinal bone growth is rapid in prenatal and early postnatal life, but then slows with age and eventually ceases. This growth deceleration is caused primarily by a decrease in chondrocyte proliferation, and is associated with other structural, functional, and molecular changes collectively termed growth plate senescence. The exact mechanism of physeal closure is not completely understood (2). Linear growth is highly regulated by endocrine factors, but a decline in growth rate does not appear to be caused by a change in hormone levels. Indeed, there is no known growth-regulating hormone whose concentration changes in a pattern that would explain the slowing of linear growth. For example, circulating insulin-like growth factor-I concentrations rise during early childhood as growth is slowing (3). Furthermore, certain disorders can cause advanced or delayed epiphyseal fusion; in patients with oestrogen deficiency it is delayed while in patients with precocious puberty it is advanced (3). Although the hormonal provocation of epiphyseal fusion is not fully defined, there are histological features that signal decreasing function. With increasing age, the overall height of the growth plate declines because of a decrease in the number of resting zone chondrocytes and the number of proliferative and hypertrophic chondrocytes per column (4). In addition, the columns of chondrocytes

become more widely spaced and the proportion of proliferative chondrocytes per column decreases(5). A loss of physeal height after trauma could indicate the early stages of physeal dysfunction. Therefore, growth plate measurement may offer a surrogate marker of posttraumatic physeal health.

1.2.2 Traumatic physeal injury

The aetiology of physeal injury is complex and can encompass both the initial trauma and a secondary surgical insult. These injuries can result in significant patient morbidity in the form of a localised or complete growth arrest. Clinically this is manifest as an evolving deformity or limb length discrepancy that, depending on location, may be poorly tolerated (Figure 1.2).

Traumatic physeal injury represents a unique challenge in paediatric trauma management. The physis is commonly implicated in paediatric fractures because its cartilaginous construct is mechanically weaker than bone and thus more vulnerable to injury. The mechanical characteristics of each layer have previously lead some to believe that certain physeal injuries are confined to specific zones. The landmark work by Salter and Harris, which bore the radiological classification, suggested that the zones of hypertrophy and provisional calcification, primarily populated by apoptotic cells and vascular channels, were commonly involved in less severe injures (Type I and II fractures) (6). They went on to suggest that more severe injuries (Type III and IV fractures) involved the entire physis, thus explaining the greater morbidity carried by these fractures. Subsequent work has demonstrated that the fracture trajectory in physeal injury is more complex than this simplistic view, with multiple zones commonly affected (7-10). However, the classification (accompanied by the more recent modification by Peterson) remains an important clinical tool providing prognostic information and guidance on treatment (Figure 1.3) (11).

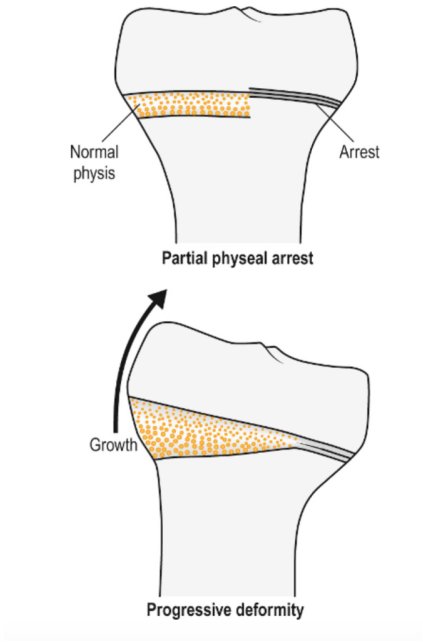

Figure 1.2: Partial growth arrest. With permission from the Authors of "McRae's Orthopaedic Trauma and Emergency Fracture Management"

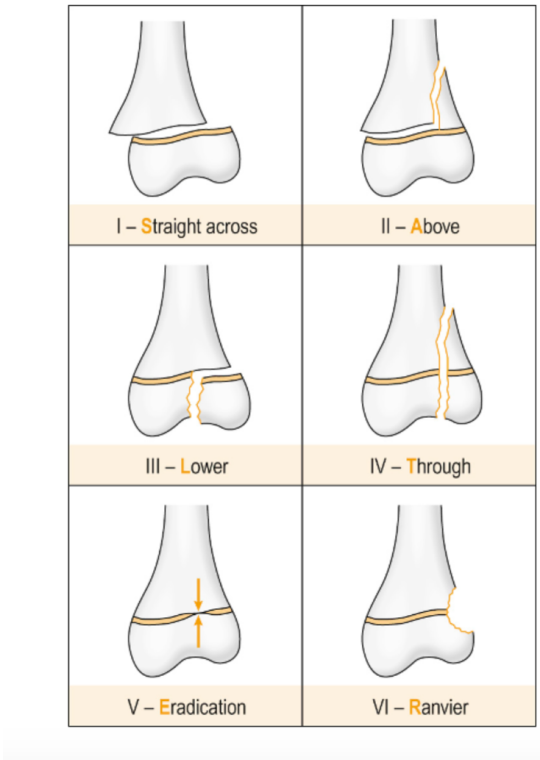

Figure 1.3: The Salter Harris classification of physeal fractures. With permission from the Authors of "McRae's Orthopaedic Trauma and Emergency Fracture Management"

Salter Harris classification

- *Type I*: characterised by a fracture plane directly through the physis with no adjacent bony injury in the epiphysis or metaphysis. Undisplaced type I injuries are therefore no different in appearance to normal radiographs except the presence of soft tissue swelling.
- *Type II*: a fracture that crosses the physis and has a variable exit through a portion of the metaphysis. The commonest physeal injury; this is often seen in the distal radius.
- *Type III*: a fracture that crosses the physis but exits through a variable portion of the epiphysis. Often associated with a higher energy mechanism, this represents an intra-articular fracture and is therefore deemed a more significant injury.
- *Type IV*: a vertical shear type fracture extending from the epiphysis, across the physis, exiting through the metaphysis. These fractures are important as they disrupt the articular surface and always affect the entire physis. The resultant displacement can lead to metaphyseal-epiphyseal cross-union(12).
- *Type V*: an unrecognised compression injury with normal initial radiographs which is only discovered after premature physeal closure has occurred.
- *Type VI*: partial, peripheral loss of the physis commonly referred to as a "lawnmower" injury, where there is a combined loss of an area of soft tissue and bone.

1.2.3 Iatrogenic physeal injury

A degree of iatrogenic physeal injury is inevitable when a device traverses the growth plate in order to achieve a stable surgical construct. Kirschner wires are the commonest fixation device in physeal fractures but a number of problems can arise during their insertion. Inappropriate soft tissue stripping and handling, unnecessary repetitive wire passage, and thermal necrosis all contribute to physeal damage. While these factors are potentially modifiable, any procedure will result in a degree of physeal injury with the potential for subsequent complications. Such complications include infection, malunion and neurovascular injury. For the purposes of this

discussion, complications will be discussed primarily in the context of supracondylar elbow fractures. Significant papers that discuss Kirschner wire fixation in other injuries are also included to provide further insight into the complications related to this implant.

Infection

Infection remains the most common complication of Kirschner wire insertion and ranges from benign, superficial wound suppuration, to deep rooted osteomyelitis causing irreparable growth plate damage. The incidence of post-operative infection varies between 0-7.9% (13-38). This variation in part relates to disagreement in the definition of pin site infection, and the clinical features that constitute the diagnosis. Ambiguity arises from the exclusion of pin site infection from the Centre for Disease Control's definition for a Surgical Site Infection (SSI) (39). Their internationally adopted reporting criteria places pin site problems under "skin" or "soft tissue" infections rather than SSI. Clarity on the clinical features that constitute a pin site infection is lacking and has led recent studies to adopt a definition first put forward by Green (38). *Major infections* are those that require admission, parenteral antibiotics or re-operation, while *minor infections* are treated on an outpatient basis with oral antibiotics or dressing regimes.

The literature detailing Kirschner wire related infections in upper limb fracture fixation is summarised in Table 1.1. The mean infection rate is 4.4% with a major infection rate of 0.8%. Two of the largest series demonstrate very low rates of infection. Bashyal *et al.* described a cohort of 622 patients with only 6 cases of infection (0.9%), while Iobst *et al.* describe a series of 304 supracondylar fractures with no infections (14, 40). Although encouraging, these results are offset by variable follow up (2-40 weeks), and high exclusion rates due to follow up out of region (117 in the study by Bashyal *et al.*). The largest study by Tosti *et al.* demonstrates a major infection rate (1.3%) more in keeping with the numerous smaller studies detailed in Table 1.1 (13). Bacteriology is sporadically reported in the literature but the majority of positive cultures demonstrated penicillin sensitive Staphylococcus aureus, followed by Pseudomonas aeruginosa, Streptococcus pyogenes, and Staphylococcus epidermidis. It is important to note that the use of

prophylactic antibiotics remains variable. Some studies describe routine use in all cases while others have found no correlation between antibiotic use and pin site infection (13, 14, 40). This is at odds with other orthopaedic procedures, such as joint replacement surgery, which demonstrate benefits in pre-operative antibiotics use. Nevertheless, antibiotic prophylaxis appears less important in Kirschner wire fixation of paediatric fractures (41).

Malunion

Malunion of displaced supracondylar distal humerus fractures most commonly results in cubitus varus. These fractures have limited capacity for remodelling due to their proximity to a slow growing physis, and can result in long term deformity. Traditionally, cubitus varus has been described as a cosmetic deformity with limited impact on function. While this may be true for the majority of cases, more significant deformities can result in chronic pain, ulnar nerve palsy, posterolateral rotatory instability and increased risk of lateral condylar and other secondary fractures (42-45). Osteotomy can provide adequate correction with good outcome but has a high rate of complication (14.9%) (46). The potential for poor outcome due to malunion, and the complications related to corrective surgery, highlight the importance of an accurate reduction and an adequate surgical construct.

Author	Year	Indication	All Infections	Major infections
Prietto et al(36)	1979	Gartland II/III	0/20	0/20
Fowles and Kassab(37)	1974	Gartland II/III	9/119	3/119
Boyd and Aronson(35)	1992	Gartland II/III	2/71	2/71
Botte et al(47)	1992	Hand and wrist fractures	10/137	3/137
Kallio et al(34)	1992	Gartland II/III	2/80	0/80
Cheng et al(33)	1995	Gartland III	2/82	0/82
Melahm et al(32)	1996	Gartland II/III and flexion type	2/115*	
O'Hara et al(31)	2000	Gartland II/III	2/31	0/31
Stahl et al(48)	2000	Wrist and hand fractures	13/234	4/234
Melham et al(30)	2001	Gartland II/III	5/198	0/198
Leet et al(29)	2002	Gartland III	1/158	0/158
Battle et al(15)	2007	Any fracture	16/202	4/202
Gosens & Bongers(28)	2003	Gartland II/III	1/200	0/200
Skaggs et al(24)	2004	Gartland II	1/69	0/69
Ponce et al(25)	2004	Gartland II/III	4/104	1/104
Foed et al	2004	Gartland II/III	3/66	0/66
Hargreves et al(26)	2004	Distal radius	12/56*	
De las Heras et al(23)	2005	Gartland II/III	3/77	2/77
Sharma et al(22)	2007	All upper limb fractures	7/105	1/105
Iobst et al(40)	2007	Gartland II/III	0/304	0/304
Skaggs et al(21)	2008	Gartland III	1/124	0/124
Eren et al(49)	2008	Gartland II/III	2/31	0/31
Bashyal et al(14)	2009	Gartland II/III and flexion type	6/662	1/662
Donnelly et al(19)	2013	Gartland II/III	4/133	1/133
Sahu(18)	2013	Gartland II/III and flexion type	7/170	0/170
Kao et al(17)	2014	Gartland II/III	44/61*	
Tosti et al(13)	2015	All wiring procedures		12/884*
		Totals	159	33
		%	4.4%	0.8%

*Comment only made on Major **or** Minor infections

Table 1.1: Reported infection rates after Kirschner wire insertion

Iatrogenic nerve injury

Iatrogenic nerve injury during supracondylar fracture fixation has a wide range of reported incidence from 1-15% (50-52). This is largely due to the choice of surgical technique, of which there are two methods: a “lateral” or a “crossed” wire technique. The lateral technique takes advantage of the lateral humeral condyle which is largely devoid of local neurological structures to place two retrograde wires. The crossed technique compliments a single lateral wire with a second inserted via the medial condyle. The intimate relationship of the ulnar nerve to the medial condyle places this neurological structure at risk (3.3%) (53-57). However, the risk is offset by an increase in biomechanical strength of the crossed wire surgical construct, which may be favoured in particularly unstable injuries (58, 59). Only a single prospective Randomised Control Trial (RCT) has used ulnar nerve injury as a primary outcome when comparing lateral and crossed wire (60). Ulnar nerve injury was minimised by the use of an open approach to the medial condyle, to allow the nerve to be identified and protected throughout the procedure. This protocol eliminated ulnar nerve injury and demonstrated that careful surgical technique can minimise iatrogenic injury regardless of the wire configuration.

1.3 POLYESTERS AS BIOABSORBABLE IMPLANTS

1.3.1 Principles of bioabsorbable implants

The development of degradable polymers for biomedical use has largely been made possible due to the demand for degradable plastics in the packaging industry. The concept of materials, with varying physical properties, that are safe for insertion into the human body, dissipate over a pre-defined time period, and leave behind only simple, inert by-products, is clearly desirable. There are three main advantages to their application in the paediatric setting.

1. No requirement for implant removal
2. Primary closure of skin at the time of surgery thus minimising infection risk compared to protruding Kirschner wires
3. Facilitation of post-operative imaging studies

In practice, the development of such materials is challenging and wrought with difficultly, particularly in predicting long term *in vivo* outcomes. The ability of a biomedical implant to achieve the aims listed above depends largely on four properties:

1. Biocompatibility
2. Degradation rate
3. Non-toxic end products
4. Mechanical strength

Biocompatibility

Biocompatibility describes the two perspectives of the relationship between an embedded implant and its surrounding tissue: (1) The effect of the polymer on tissue and (2) the effect of the tissue on the polymer. For a material to be considered safe for human use, whether an orthopaedic implant, a hernia mesh or drug delivery vehicle, it must be biocompatible. In the case of a bioabsorbable implant, which undergoes degradation over time, biocompatibility serves to describe not only the immediate effects of the implant/tissue interface but also the reaction to any

degradation by-products or the eventual end products. Each of these components must cause negligible harm to local and systemic tissues for that implant to be deemed biocompatible.

Degradation

Degradation of a polyester occurs through hydrolysis – the exposure of the surface to water molecules, resulting in cleavage of the ester bond and the production of acid and alcohol products. The amorphous (poorly organised) regions are more susceptible than those of a more crystalline (highly organised) structure. Initially the amorphous regions absorb water and degrade at a constant rate, until breakdown is expedited by a secondary phenomenon. Autocatalysis occurs due to the production of low molecular weight polymer products (oligomers) with a free acid group. These molecules cause further breakdown of larger polymer chains to compliment the catalysis caused by the presence of water. Therefore, the second stage of degradation is more rapid and leads to loss of structural integrity with the formation of cracks and voids. The rate and extent of this biodegradation is dependent on three factors (1) polymer-dependent properties, (2) environmental factors and (3) implant size and shape.

The process by which the polymer is formed contributes to its subsequent behaviour. Catalysts used to promote polymerization, particularly those that encourage hydrophobic qualities, can increase resistance to degradation while the presence of impurities, or those polymers with low molecular weight, increases susceptibility (61). Most important is the level of crystallinity; those polyesters with a higher ratio of crystalline to amorphous regions. These polyesters absorb less water which makes them less susceptible to hydrolysis, slowing the degradation process. Lastly, polymers that are engineered with a lower porosity resist initial degradation and are therefore slower to dissolve.

Environmental factors are perhaps the least important determinant of degradation as they cannot be manipulated to create advantage and are constant. Temperature has a direct relationship with degradation rate, although has no effect on mechanism of this

process (62). The effect of local pH is less clear with some studies suggesting an increase in rate, while others postulate a decrease (63).

The implants macroscopic structure plays a prominent role in degradation qualities. Thickness is perhaps the most critical component due to its influence on the rate of autocatalysis. Surface degradation in thicker implants, leads to oligomers that become trapped and penetrate the middle of the implant, initiating degradation from within. Thinner products do not share this property as the excess oligomers can be diffused into the surrounding water due to their higher surface area to volume ratio (64). Lastly, the method of implant manufacturing influences properties where processes such as hot moulding and cold compression create differences in porosity and therefore biodegradation (65, 66).

Regardless of the chosen polymer or implant design, the products of the degradation process must be of limited toxicity. It is know that the acidic degradation products formed during hydrolysis can significantly lower the local pH which may result in toxicity due to the formation of free radicals (67). Large orthopaedic implants could generate concentrations of acidic oligomers that may have negative effects, although this has not been proven.

Mechanical strength

If a dissolvable implant can satisfy the conditions discussed above (biocompatibility, appropriate degradation process and benign end products) attention may turn to its mechanical properties. The mechanical strength of a polyester is of particular concern in the field of orthopaedic trauma, where an implant must be able to provide structural stability. The long bones are subjected to dynamic forces of varying magnitude and vector, and the demands placed on plates and screws used for fixation are significant. Traditionally, stainless steel is employed due to its strength, durability and low cost. Polyesters not only have limited strength compared to steel, but they also appear to degrade faster under the demands of fracture fixation (68, 69). As such their time-dependent dissolution, which also represents their most attractive property, remains a concern. To be considered a mechanically viable option in the

trauma setting, a polyester must maintain sufficient mechanical strength until fracture union.

1.3.2 Polyesters

PGA

Polyesters have gained the widest interest for biomedical use as they can be formed to produce an array of compounds with varying physical, chemical and mechanical properties. Poly(glycolic) acid (PGA) is a highly crystalline polymer (>50%), that has a high mechanical strength with a Young's Modulus of 12.5 GPa. It was the first synthetic biodegradable polymer introduced for medical use, under the trade name Dexon® in 1969. To complement its high strength, PGA demonstrates a relatively rapid dissolution due to the polymers hydrophilicity. These properties inspired its use as the first dissolvable suture. To optimise the strength and degradation characteristics of PGA, co-polymers were subsequently produced. Vicryl® is perhaps the most widely recognised co-polymer in surgical practice, made by the introduction of L-lactide into the polymer mix, providing a longer period of maximal strength before breakdown. While biodegradable polymers were considered primarily as a suture material, the favourable properties of PGA and poly(L-lactic) acid (PLLA) lead to their expended use.

PLLA

Lactic acid is the starting material of PLLA and can be produced biologically or chemically. The biological approach utilises the fermentation of carbohydrates by an engineered *lactobacillae* strain and is considered more cost effective than the chemical approach. Different strains of *lactobacillae* produce either the predominantly D or L isomer of lactic acid (PDLLA or PLLA); L-lactic acid is the naturally occurring isomer that is produced in muscle during anaerobic respiration(70). Dimerization (the joining of two molecular subunits) of lactic acid yields lactide which is then used for the production of PLLA. Polymerization of L-lactide leads to the formation of a semi-crystalline polymer with a degree of crystallinity of approximately 40%. Despite a lower crystallinity than PGA, PLLA

has a relatively high modulus of 4.8GPa with favourable tensile strength. Those polymers composed of PDLLA have a lower Modulus, and a high proportion of amorphous polyester resulting in reduced strength and more rapid degradation. While not considered in the orthopaedic sphere, they may be used in drug delivery systems or tissue scaffold where these properties are desirable (69). The mechanical properties of PLLA are complemented by a degradation rate that can exceed bone healing time. Furthermore, PLLA produces benign end products (71). It is hydrolysed by random back bone scission of the polymer chains which is initially slow due to the high crystallinity of the polymer. The end product is lactic acid, a naturally occurring substance, that participates in the Krebs cycle and is excreted as CO_2 and H_20.

In vitro properties of PGA and PLLA

The *in vitro* effects of PGA and PLLA have been extensively studied in numerous animal models (rat, sheep, goat and pigs) to gain insight into potential human application. Research in the 1970s focused on degradation and biocompatibility. A large study by *Miller et al* placed small bars of polyester of varying PGA:PLA ratio in the abdominal subdermis or femoral cavity of 420 rats (72). It was the first study to demonstrate that *in vitro* degradation rate could be manipulated by changing polymer ratio and also showed that bars composed of 100% PLLA were still intact after the 12-month end point. Further works added insight into polyester biocompatibility by assessing inflammatory reactions when PGA and PLLA compounds were implanted into subcutaneous or muscular tissue. Rat and rabbit models demonstrated relatively frequent minor local inflammatory responses but very few significant issues, with a propensity for PGA driven reactions (71, 73-77). These works have been complimented by studies which have assessed the inflammatory response to PLLA placed within the intra-medullary canal of rabbits (71, 78, 79). No significant inflammatory reactions were demonstrated with *Fini et al* commenting that histology showed no inflammatory cells or resorption of bone trabeculae. Development of fracture models subsequently assessed the suitability of PGA and PLLA for fixation. The use of a rabbit distal femur lateral unicondylar osteotomy (creating an AO ‘B’ type intra-articular fracture) was often employed as it

allows assessment of fracture healing without placing undue demand on the polymer implant due to the local bony support through the intact medial condyle. Successful fracture healing was demonstrated in the four major studies which were complimented by smaller studies in sheep and dogs (80-85). From these works it was theorised that polyester implants could offer a safe alternative to those composed of metal for certain clinical applications.

1.4 THE CLINICAL HISTORY OF BIOASORBABLE IMPLANTS IN ADULTS

1.4.1 Early developments

The successful implantation of polyesters into various animal model lead to their introduction in human surgery. In 1971, biodegradable materials were first reported for the fixation of cranio-facial fractures (86). Clinicians in the Soviet Union appeared to have been early adaptors of the technology with a large review in 1984 discussing the merits of bioabsorbable co-polymers, with numerous case studies highlighting their efficacy in fracture fixation (87). Enthusiasm for fracture fixation with bioabsorbable implants continued with ankle fracture fixation using rods of Vicryl® (PGA: PLA ratio 90:10) reported in Finland in 1985 (88). These early developments illustrated the potential of these implants for bony fixation and lead to their subsequent use in a number of surgical fields. The outcomes in each surgical speciality offers insight into the potential use of bioabsorbable implants in the paediatric setting.

1.4.2 Cranio-maxillofacial surgery

Steel plates have been the standard of practice since the early developments in maxillofacial fracture surgery, with removal a routine secondary procedure (89). This need for removal along with their subcutaneous nature and adherence to local tissue lead to early interest in absorbable implants. The use of PLLA/PGA co-polymer panels was first established as a means of treating the bony deficit in orbital floor blow out fractures and craniosynistoses (90-94). Initial success led to extended indications for use to include mandibular fracture fixation. Fixation in the mandibular region represents a greater challenge than procedures in the mid face as the osseous fragments are exposed directly to mastication load and movement. A large prospective study comparing the efficacy of co-polymer plates to those made from titanium was undertaken in 2008. The INION® system utilises plates and screws of PDLLA co-polymers and was used to secure 30 mandibular fractures (95).

Patients were assessed for fracture healing, malunion (in this case the occurrence of jaw malocclusion) and were regularly reviewed for signs of wound dehiscence or inflammatory response. All fractures healed uneventfully however there was an increase in malocclusion in the INION® group – this demanded a change in post-operative protocol by the introduction of temporary elastic inter-maxillary fixation. Although this modification brought the rate of malocclusion in line with titanium plates, it highlighted the inferior strength of polyester implants. There was no difference in wound healing/complication rate although four patients with the INION® plates continued to have a dense swelling over the operative site at 6 months due to plate degradation. However, they concluded that the system was biocompatible and strong enough for the demands of mandibular surgery. Further studies have highlighted the effective use of bioabsorbable implants in facial and mandibular surgery but warn of the risk of foreign body reaction (89, 96, 97).

The evidence contributed by the field of cranio-maxillofacial surgery offers insight into the potential uses for the bioabsorbable implants in orthopaedics. Thin (2mm) plates and screws demonstrated sufficient mechanical strength for use in fracture fixation, with acceptable rates of complication. However, these results cannot be directly extrapolated to surgery in the appendicular skeleton. The implants would be larger, the forces experienced greater, and regions with a high proportion of cortical bone may be encountered.

1.4.3 Sports surgery

Bioabsorbable implants have gained wide use in the field of sports surgery, particularly in the shoulder and knee. The use of polyesters as suture anchors, interference screws, and in meniscal repair systems have all been explored with varying success

Shoulder

Surgery for traumatic shoulder instability, in the absence of significant bony injury, consists of soft tissue repair and anterior capsule plication. The reconstitution of the labrum is key to reinstating long term stability, and is achieved through the use of

suture anchors in the anteroinferior glenoid. Suture anchors are relatively small devices, however, three or more are often required resulting in the loss of bone volume within the anterior glenoid rim. Absorbable anchors could potentially allow the restoration of bony tissue after resorption, with the added benefits of minimal artefact during repeat imaging (commonly required in shoulder instability) and less morbidity if loosening occurs. Their clinical performance has been assessed in numerous studies with three large randomised controlled trials demonstrating comparable performance to metal implants (98-100). All trials made comment on the appearance of radiographic bone holes at the end of the study period (24-30 month follow-up). Evidence of the drill hole was found in the majority of patients suggesting the anchors had yet to resorb or had caused a cyst to form. It is worthy to note that cyst formation is not restricted to absorbable implants and can also be a consequence of metal anchors (101). A 7 year follow up study on the randomised trial performed by *Ejerhed et al* showed that 67% of patients had invisible or hardly visible drill holes while benefitting from shoulder stability comparable to other long term studies (102). These works serve to demonstrate the potential success of bioabsorbable implants and prove the occurrence of anchor absorption with bony infilling.

Knee

The use of bioabsorbable polymers for interference screws in ACL reconstruction graft fixation is perhaps the most commonly accepted example of their clinical application. Minimising the need for implant removal, while advantageous in all parts of the body, is particularly helpful in this setting. This is for three main reasons; locating and removing the screws (particularly in the femoral tunnel) is challenging, revision ACL surgery need not be concerned with tunnel placement as drilling will easily bypass any old screws, and polymer screws can easily be cut if there is an eventual need for knee arthroplasty. A number of RCTs comparing metal and absorbable interference screws in adults have been undertaken, but focus on early outcomes and complications rather than the potential long-term benefits mentioned above (103-105). A recent Cochrane review assessed the evidence and suggested that there is little difference in self-reported knee function and levels of activity between

bioabsorbable and metallic interference screws (106). There is very low-quality evidence that bioabsorbable screws may be associated with more overall treatment failures, including implant breakage during surgery, but they remain in common use.

More recent work has used Magnetic Resonance Imaging (MRI) to assess interference screw dissolution and bony ingrowth. Drgoset *et al.* measured screw resorption and bone-patella-bone graft integration two years postoperative (107). A reduction of 63% and 64% was seen in the femoral and tibial screws respectively. Bony integration of the bone block was considered good in 90% of patients and fair in 10% patients. This provides further evidence that, over time, PLLA implants will resorb and allow regrowth of bone into the defect.

1.4.4 Adult Trauma

The use of bioabsorbable implants in trauma is of particular interest due to high rates of implant removal. Certain fractures necessitate the insertion of plates over areas of bony prominence which can result in irritation and ongoing morbidity. The concept was extensively explored by Bostman and colleagues in their series of over 30 papers in the 1980s, 1990s and 2000s (80-82, 88, 108-133). Publications included animal studies, reports of complications, several review articles and a randomised trial. The human studies often focussed on the outcomes of an expanding group of patients that had ankle fixation with bioabsorbable rods between 1985 and 1994. The papers in 1985 and 1987 first described the initial randomised control trial of ankle fracture fixation, comparing traditional plates and screws with intra-medullary PGA/PLA 9010 (Vicryl®) rods (88, 108). The rods were self-reinforced with Vicryl® suture material passing through their length and were used to fix uni-malleolar and bi-malleolar fractures (lateral malleoli were secured by passing the rod in a retrograde, intra-medullary fashion). The operative reduction, its maintenance until healing, and post-operative complications were comparable between the two groups. While there were no infections in the bioabsorbable group, two patients developed a sterile sinus most likely due to expulsion of degradation products. This is the first documented occurrence of such a complication in the orthopaedic literature and it remains a common source of uncertainty in bioabsorbable implants (see section 1.5). However,

the authors were so influenced by the early success that they concluded the article by stating that the new method of fixation had become the standard of practice within their unit. Subsequently, the cohort of ankle fractures increased considerably and by the end of the 1990s two further papers detailing the outcomes of over 2000 patients were published (125, 129). Importantly, both papers drew attention to an increased rate of adverse soft tissue reaction when using PGA rods, which drove the development and implementation of PLLA implants. This lead to a higher rate of good/excellent outcomes (129, 130).

Since the trial by *Bostman et al.* a number other RCTs have been published assessing the performance of PLLA implants in adult fracture fixation (134-140). Three randomised trials compared the outcomes of patients with a distal tibiofibular diastasis treated with a metal or PLLA screw (135, 138, 140). Any associated lateral malleolar fracture was fixed with a metal plate, through which the PLLA or metal screw was inserted. All injuries healed with no radiological difference in the syndesmosis between the groups, with the authors stating that the PLLA screws significantly reduced the need for secondary procedures. However, the studies share a rather glaring design flaw; all metal screws were removed at 8-12 weeks. Therefore, the suggested benefit of the of the PLLA screws is somewhat overstated due to the routine practices of the participating units. This flaw was addressed in the trial by *Noh et al.* who compared traditional methods of fixation with PLLA plates and screws for bi- and tri-malleolar ankle fractures (136). 109 patients were enrolled and followed up for one year with clinical, radiographic and patient reported outcomes. Operative time was significantly longer in the PLLA group (30.2 vs 56.4 minutes, $p < 0.001$) which was attributed to the complexities of the plating system, although this did not result in any differences in the American Orthopaedic Foot & Ankle Society (AOFAS) ankle-hindfoot scales or Short Musculoskeletal Functional Assessment dysfunction/bother index scores. Two cases of fibular non-union occurred in the PLLA group due to pull out of the distal screws from the fibula. The authors suggest that this occurred due to poor screw design (small screw pitch, small screw core/thread ratio) rather than any inherent weakness of the polymer. Despite these complications (which were not deemed statistically significant) the study concluded

that the PLLA implants were comparable to those consisting of metal and were suitable for widespread use. Similar results were borne out in more recent works where two small, underpowered studies assessed absorbable plates and screws (134, 139).

Zhang et al. have published the only RCT investigating an injury out with the ankle: intra-articular fractures of the calcaneus. Metal plates and screws were compared to bioabsorbable screws, with similar radiographic and patient reported outcomes at one year (137). Bioabsorbable implants minimised soft tissue complications and the need for secondary procedures (1 vs 5). However, the comparison of two differing fixation philosophies, one with a plate (metal group) and one with only screws (PLLA group), draws doubt over the results of this study. Calcaneal plates are relatively bulky, and comparing their outcome with a surgical technique that utilises only screws is flawed. The benefits described in using PLLA screws may well be achieved with those of metal.

From these studies, it is clear that Level I evidence on PLLA implants in trauma is limited and frequently flawed. Each study offers insight into the potential merits of this technique but only the study by *Noh et al.* is without a significant design weakness. In attempts to clarify the available evidence, two groups have performed meta-analyses (141, 142). Both have focussed on ankle fractures (with or without syndesmotic disruption) and conclude that outcomes are comparable with no statistically significant difference in overall complications. However, *Van der Eng et al.* state that the absolute number of complications was greater with bioabsorbable screws. This raises the concern that the incidence of complications with bioabsorbable screws has been understated, as the limited evidence has insufficient power to demonstrate statistically significant findings.

1.5 ADVERSE SOFT TISSUE REACTIONS TO BIOABSORBABLE FRACTURE FIXATION IMPLANTS

A primary concern in the use bioabsorbable implants is the potential for an adverse soft tissue response. Within a few years of their introduction, it was realised that these materials are sometimes associated with a method specific soft tissue reaction that has the characteristics of a foreign body inflammatory reaction (110, 113, 143-145).

1.5.1 PGA

The reactions were particularly prominent in the early use of PGA, where patients developed a painful papule or discharging sinus 2-4 months after operation. The largest series of patients with PGA fracture fixation was reported in 2000 (129). 2037 patients had undergone treatment, the majority of whom sustained an ankle fracture (47%), with 107 suffering a foreign body reaction (5.7%). This occurred on average 79 days after insertion as a suddenly emerging painful, erythematous, fluctuating papule over the implant track. Unless immediately aspirated or incised, the papule usually burst within a few days and left a sinus discharging liquid remnants of the disintegrated implant. The mean duration of the discharge was 6 weeks (range: 2-27 weeks). The lesions were treated by debridement under local or general anaesthesia. In addition to the soft tissue reaction, 57% of the patients had radiographic evidence of osteolysis. Several markers of increased risk were found: the use of Quinone dye within the implant, poorly vascularised bone (such as the scaphoid), and a high implant surface area (screws worse than rods). The paper does not discuss other complications, such as infection, that occurred during the study period and it is therefore unclear if PGA implants significantly increased the overall complication rate (146). The potential for PGA pins to reduce infection and therefore offset the additional risk of sterile soft tissue reactions, was not defined.

While it could be argued that an incidence of 5.7% is relatively low, other studies contradict this result and report higher rates of adverse soft tissue reactions (Table

1.2). In particular, a randomised control trial comparing Kirschner wires to PGA rods for distal radius fixation found a rate as high as 47% (147). In order to provide a clearer understanding of the clinical implications, a classification system was developed and suggested three types of reaction (128):

- ***Mild***: a painful erythematous papule
- ***Moderate***: a sinus discharging polymeric debris for up to 6 months
- ***Severe***: extensive osteolytic lesions

However, the terminology of this system is somewhat flawed, with surgeons unlikely to agree that the presence of a sinus over a surgical wound for 6 months, could be deemed "moderate". This is demonstrated in a number of subsequent papers which reported clinical outcomes but did not adhere to the suggested classification. Instead, most studies comment on whether the soft tissue reaction resulted in a full thickness breakdown of the dermis. Table 1.2 summaries the available evidence on PGA implants for fracture fixation, with the adverse reactions categorised into ***minor*** (reaction with intact overlying skin) and ***major*** (skin breakdown, regardless of the requirement for intervention). A major rate as high as 25%, with a minor rate of 33%, lead to scepticism over the use of PGA in fracture fixation. Even the early enthusiasm from Bostman and colleagues was tempered, with a clear tonal change in later articles from the group. Rather than espouse the benefits of PGA implants, caution was promoted with the suggestion that further research was needed. PGA fell from favour and an alternative polymer began to be used in the clinical setting: PLLA.

Polymer	Author	Year	Patients	Study type	Fracture	Implant type (Rods >2mm, pins <2mm)	Follow up (Months)	Number of adverse reactions (%)	
								Minor	Major
PGA	Bostman(109)	1989	102	RCS	Ankle	Rods	12	0 (0%)	6 (5.8%)
PGA	Hirvensalo(148)	1989	41	RCS	Ankle	Rods	12-32	3 (7%)	3 (7%)
PGA	Bostman(110)	1990	516	RCS	Various	Rods	2-18	0 (0%)	41 (7.9%)
PGA	Hirvensalo(111)	1990	24	RCS	Radial head	Pins	28	NC	2 (8.3%)
PGA	Barfod(143)	1992	2	CR	Intra-articular knee	Pins	4	NC	2 (100%)
PGA	Castelyn(147)	1992	15	RCT	Distal radius	Rods	12	1 (6.7%)	6(40%)
PGA	Friden(145)	1992	1	CR	Osteochondral knee	Pins	4	NC	1 (100%)
PGA	Frokjaer(149)	1992	25	PCS	Ankle	Rods	12	0 (0%)	1 (4%)
PGA	Partio(115)	1992	152	PCS	Ankle	Screws	19-46	NC	10 (6.5%)
PGA	Kankare(150)	1995	16	PCS	Ankle	Screws	12	1 (6%)	2 (12%)
PGA	Peito-Vasenius(119)	1995	20	RCS	Scaphoid non-union	Pins	57-77	NC	5 (25%)
PGA	Hovis(151)	1997	21	RCS	Ankle	Screws	8-16	7 (33%)	1 (4.7%)
PGA	Kankare(152)	1997	6	RCS	Tibial condyle	Screws	12	NC	1 (16%)
PGA	Tuompo(153)	1997	13	RCS	Osteochondral knee	Pins	12-84	NC	1 (7.6%)
PGA	Kanare(154)	1998	25	PCS	calcaneus	Rods/Pins	11-38	0 (0%)	3 (12%)
PGA	Bostman(129)	2000	2037	RCS	Various	Pins/rods/screws	Up to 120	0(0%)	107 (5.3%)

Table 1.2: Adverse soft tissue reactions to PGA in adult fractures. Retrospective Cohort Study (RCS), Prospective Cohort Study PCS), Case Report (CR), Randomised Control Trial (RCT). Not commented (NC) Minor adverse reaction: swelling or erythema, Major adverse reaction: sinus formation or operative debridement.

1.5.2 PLLA

The majority of research since the late 90's has concentrated on polymers or co-polymers composed of PLLA. Numerous studies have reported the radiographic and clinical outcomes from PLLA fracture fixation and are detailed in Table 1.3. The largest was the second component of the cohort study by *Bostman et al.* in 2000 (129). Having established the inherent risk in the use of PGA, they commenced the use of PLLA implants in 491 patients. The rate of sterile soft tissue response was significantly lower, with only one case that required a secondary procedure for debridement. Subsequent works mainly focussed on fixation of ankle fractures and/or distal tibiofibular diastasis. The majority report a similarly low incidence of soft tissue reactions supporting the assertion that PLLA is a more suitable polymer than PGA (134, 136, 137, 139, 140, 155-157).

Adverse soft tissue reactions occur through the accumulation of excess polymeric debris, a phenomenon that is more likely to coincide with periods of increased degradation. At a certain point, the intended structure of the implant is lost which provides a higher surface area for breakdown reactions and can lead to excess debris. Initially authors felt that the degradation profile of PLLA would mitigate the potential for debris accumulation, as the slower rate would not overwhelm the capability of local tissues to process by-products (128). However, others contended that maximal debris production would simply occur later, and that the clinical presentation of an adverse reaction would be delayed rather than eliminated. The first report of a late foreign body reaction to PLLA was published in 1998 (126). A patient who had undergone bi-malleolar ankle fracture fixation, presented 52 months post-operatively with a painful papule over the lateral side. Surgical excision was required due to persistent symptoms with histology confirming the presence of multiple macrophage cells surrounding, and also containing, polymeric particles. The fact that the late foreign-body reaction occurred only on the lateral side of the ankle suggests that the response represented a local overload of polymeric debris rather than an immunologically mediated sensitivity to the polymer. This case study draws doubt over the relevance of a number of articles published on PLLA implants

with limited follow up. Only seven studies detail outcomes between years 4 and 5 post-operative, with only two of these having reviewed all patients at this time point (Table 1.3). The incidence of minor (0-22%) and major (0-40%) reactions varies widely. It is worth noting that studies without at least 4 years follow up regularly reported no reactions, while those with over 4 years reported at least some minor or major reactions. This suggests that limited follow up results in underreporting of adverse soft tissue reactions related to PLLA implants.

Only the works by *Bucholz et al.* and *Sun et al.* present Level I evidence with follow up over 4 years (138, 158). Although both detail the outcome of PLLA screws used to stabilise the distal tibiofibular syndesmosis, their outcomes are dissimilar. *Bucholz et al.* report only one major reaction (1.2%) while *Sun et al.* encountered 18 minor (22%) and 8 major (9.7%) reactions. The reason for this difference is not apparent as both studies use similar protocols and polymers. Nevertheless, both serve to demonstrate that a degree of late soft tissue reaction must be expected when using PLLA implants in trauma surgery. Whether this risk is offset by the advantages of bioabsorbable implants remains unclear.

Polymer	Author	Year	Patients	Study type	Fracture	Implant type (Rods >2mm, pins <2mm)	Follow up (Months)	Number of adverse reactions (%)	
								Minor	Major
PLLA	Bucholz(158)	1994	83	RCT	Ankle	Screws	60	0(0%)	1 (1.2%)
PLLA	Yamamuro(159)	1994	43	PCS	Various	Screws /pins	12-72	NC	1 (2.3%)
PLLA	Bostman(118)	1995	51	RCS	Ankle	Screws	37-69	1 (1.9%)	3 (5.8%)
PLLA	Eitenmuller(160)	1996	7	RCS	Ankle	Pins and plates	24	NC	0 (0%)
PLLA	Matsusue(161)	1996	5	CR	Osteochondral	Pins	24-84	NC	0 (0%)
PLLA	Bostman(129)	2000	491	RCS	Various	Pins/rods/screws	Up to 120	0(0%)	1 (0.2%)
PLLA	Thorasden(140)	2001	17	RCT	Syndesmosis	Screws	11	0(0%)	0(0%)
PLLA	Sinisaari(162)	2002	20	PCS	Syndesmosis	Screw	12	0(0%)	0(0%)
PLLA	Kaukonen(135)	2005	20	RCT	Syndesmosis	Screws	35	0(0%)	0(0%)
PLLA	Dumont(163)	2007	14	RCS	Metacarpal	Plates / screws	26	3 (21%)	0(0%)
PLLA	Joukainen(139)	2007	31	RCT	Ankle	Screws	12	0(0%)	0(0%)
PLLA	Givissis(164)	2008	25	RCS	Radial head	Pins	60	0(0%)	0(0%)
PLLA	Givissis(165)	2010	10	RCS	Metacarpal	Plates/screws	34-61	2 (20%)	4 (40%)
PLLA	Noh(136)	2012	49	RCT	Ankle	Plates/screws	12	0(0%)	0(0%)
PLLA	Zhag(137)	2012	47	RCT	Calcaneus	Screws	23	0(0%)	0(0%)
PLLA	Bassuener(157)	2012	78	RCS	Peri-articular	Pins	12	0(0%)	0(0%)
PLLA	Sun(138)	2014	82	RCT	Syndesmosis	Screws	55	18 (22%)	8 (9.7%)
PLLA	Gaiarsa(134)	2015	10	RCT	Ankle	Plates/screws	9	0(0%)	0(0%)
PLLA	Xiong(156)	2015	5	RCS	Metacarpal	Pins	4	0(0%)	0(0%)
PLLA	Zhao(155)	2016	56	PCS	Cervical spine	Screws	12-48	0(0%)	0(0%)

Table 1.3: Adverse soft tissue reactions to PLLA in adult fractures. Retrospective Cohort Study (RCS), Prospective Cohort Study PCS), Case Report (CR), Randomised Control Trial (RCT). Not commended (NC). Minor adverse reaction: swelling or erythema. Major adverse reaction: sinus formation or intervention required.

1.6 TRANSPYSEAL BIOABSORBABLE IMPLANTS

The use of dissolvable implants is particularly attractive in the paediatric setting where secondary removal procedures are more distressing. However, the need to traverse the growth plate during fracture fixation introduces the potential of physeal damage and a resultant growth abnormality. There is limited animal or human evidence evaluating the safety or efficacy of transphyseal absorbable implants.

1.6.1 Animal models

While numerous animal studies have assessed the physeal response to injury, few investigate the effects of polymer interposition (166-171). In 1989 *Makela et al.* were the first to detail the outcomes of physeal penetration with a bioabsorbable device (172). 50 rabbits had a polydioxanone (PDS) rod of varying caliber inserted in a retrograde fashion through the distal tibia physis. Leg length, joint orientation and physeal histomorphometry were compared to a control consisting of drill holes on the contralateral limb. The 2mm rods were estimated to have invaded 3% of the growth plate, while the 3.2mm rods affected 7%. This translated to a statistically significant difference in outcome: the smaller pins did not affect femoral length while the 3.2mm rods reduced growth and caused bony bar formation. Rod breakage was evident in all specimens at 6 weeks despite the implant having no structural responsibility. This study had two important conclusions; it demonstrated the ability of the physis to compensate for a degree of destruction through the growth of the remaining healthy sections, whilst indicating that PDS should not be considered for fracture fixation due to poor mechanical properties. Subsequent work assessed the physeal response to PGA and demonstrated that its interposition did not cause any additional physeal damage when compared an empty drill hole of equal bore (173). Only one animal study has assessed the outcome bioabsorbable fixation of a simulated physeal fracture. In 1980 Makela *et al* created a Salter Harris I fracture in rabbit distal femora which were secured with two PGA rods(174). The rods provided sufficient mechanical stability to allow healing with growth abnormality.

The limited evidence on the effects of bioabsorbable rods on the physis suggests these implants are relatively benign and do not cause growth abnormality. This, in conjunction with the success of bioabsorbable implants in adult fracture fixation, led to their use in the paediatric population.

1.6.2 Clinical studies

Makaela *et al* followed their animal work with the first publication detailing outcomes of bioabsorbable pins in paediatric physeal fractures (175). 19 patients had 1.7mm self-reinforced PGA pins inserted to secure either a supracondylar fracture, lateral condyle fracture or medial epicondyle avulsion. Follow up was between 6-26 months with good radiographic and clinical outcomes in all patients. This was followed by a small number of subsequent cohort studies that have assessed the outcomes of transphyseal bioabsorbable fixation (Table 1.4). Patient numbers are generally low with no RCTs and only one prospective trail. The majority report good outcomes with minimal growth disturbance, malunion or infection. The study by Bostman in 1993 is notable as the only prospective study and reports a high rate of malunion in supracondylar fractures (7%). Three of the 45 supracondylar factures included in their study demonstrated pin breakage with severe displacement and a requirement for further surgery. They conclude that while bioabsorbable pins may be suitable in the other fractures included in the paper, their use in the supracondylar region should be approached with caution. Interestingly, the same author was involved in a subsequent paper by Rokkanen in 2000 (130). This paper detailed the outcome of a number of adult and paediatric fractures fixed with PGA/PLLA implants between 1987 and 1991. The use of bioabsorbable implants in paediatric elbow injuries was advocated but the authors did not mention if the cohort from the previous paper was included, nor do they offer an explanation for a change in surgical recommendation.

The follow-up in studies assessing transphyseal PGA/PLLA implants is variable and often relatively short (Table 1.4). As discussed in the section 1.5.2, adverse PLLA reactions can occur up to 4 years after insertion; only three studies include follow up beyond that time point (176-178). No adverse soft tissue reactions were recorded,

and while this is encouraging, it is tempered by the low numbers and retrospective nature of these studies.

The literature detailing the use of transphyseal bioabsorbable implants for fracture fixation is encouraging but limited. Further work is required to define the effects of these polymers on the growth plate and any effect they have on growth.

Author	Year	Study type	injury	Patients	Implant type	Follow up (months)	Malunion	Growth disturbance	Infection	Adverse reactions
Maekela(175)	1992	RCS	Elbow	19	PGA pins	17	0	0	0	0
Bostman(117)	1993	PCS	Various	71	PGA pins	16	9	0	NC	NC
Svennsson(179)	1994	PCS	Various	50	PGA pins	18	0	0	0	0
Rokkanen(130)	2000	RCS	Various	140	PGA pins	Not defined	4	0	2	3
Podezwa(180)	2008	RCS	Ankle	24	PLLA screws	5	1	2	0	1
Fu(178)	2011	RCS	Elbow	56	PLLA screws	48	0	0	0	0
Andrey(177)	2013	RCS	Elbow	5	PGA pins	52	0	0	0	0
Takada(176)	2013	RCS	Elbow	8	PLLA pins	53	0	0	0	0
Fuller(181)	2016	RCS	Radial neck	7	PLLA pins	9	0	0	0	0
Su(182)	2016	RCS	Radial neck	68	PLLA pins	41	0	0	0	0

Table 1.4: Transphyseal fracture fixation with bioabsorbable implants. Retrospective Cohort Study (RCS), Prospective Cohort Study (PCS).

1.7 THE BIOTRAK HELICAL NAIL

The Biotrak Resorbable Fixation System (Acumed®, Hillsboro, Oregon) is a family of implants produced for the fixation of upper and lower limb fractures, fusions and osteotomies. A number of devices are available within the product range but all are composed of pure PLLA. As with all PLLA implants, it is intended to degrade fully between 2-5 years.

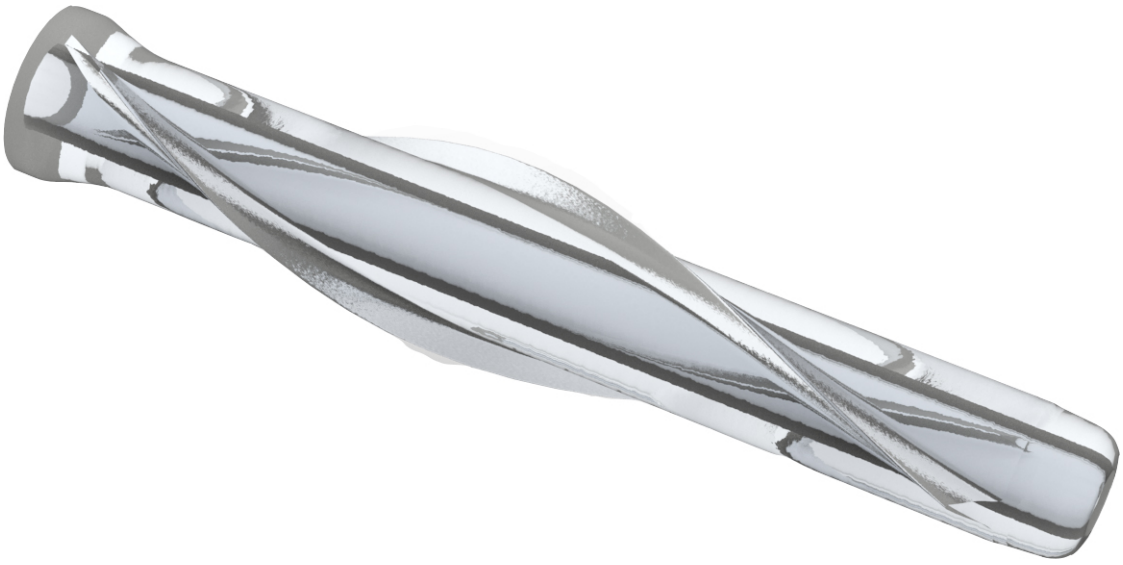

Figure 1.4: The Helical Nail

The Helical Nail is a cannulated, cylindrical implant with variable pitch flutes (Figure 1.4). It functions as a smooth pin that can be tapped into place after reaming over a standard 1.1mm guidewire. The flutes are intended to provide some compression during insertion, similar to established metal implants with a variable pitched thread (Figure 1.5).

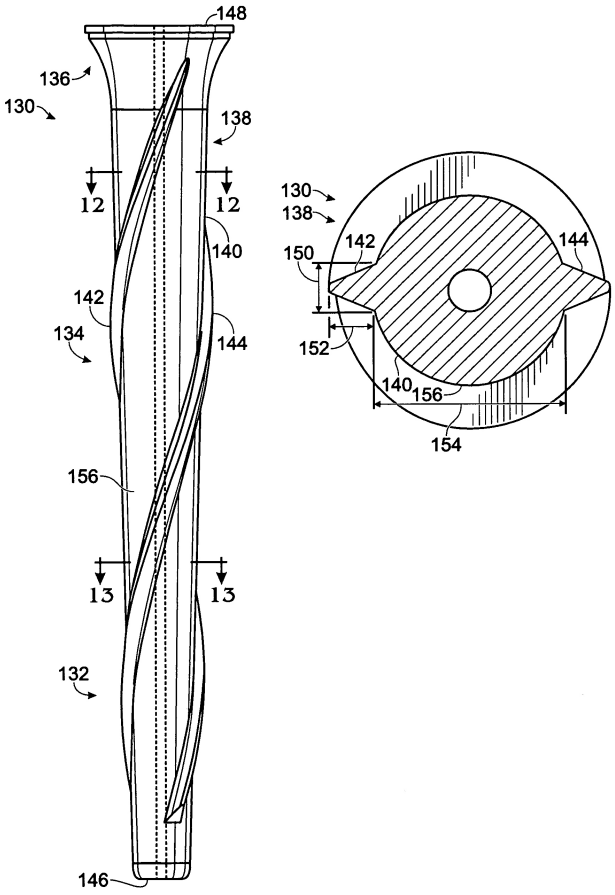

Figure 1.5: Helical Nail schematic. Drawing from US patent 8,092,505 detailing the dimensions of the Helical Nail and the variable pitch flutes. The left hand image is side on while the right hand image is in cross section.

The Helical nail is 2.5mm wide and comes in lengths of 20mm, 30mm and 40mm, although the implant can be trimmed after insertion to ensure there is no protuberance. The Helical Nail is currently licenced for fixation and/or alignment of fragments and fractures of non-load-bearing bones, osteotomies, arthrodesis, cancellous fragments, and osteochondral fragments in the upper and lower extremities.

1.8 THE KEY QUESTIONS

The use of the Helical nail in paediatric fracture fixation would allow primary skin closure at the time of insertion, in order to minimise post–operative infection, and negate the need for removal. This study had three components, each designed to address a question relating to the use of this device in the paediatric setting:

1. What is the complication rate of Kirschner wire fixation in the local population, and does this warrant the introduction of a new surgical method?
2. Is the Helical Nail mechanically comparable to Kirschner wires?
3. Does the Helical Nail affect the growth plate, and if so, does this result in limb length discrepancy?

1.9 HYPOTHESIS

The Biotrak Helical nail is mechanically comparable to the current clinical standard of Kirschner wires. It does not cause significant growth plate injury or retardation of limb growth.

Section 2: Surgical complications of Kirschner wire fixation of supracondylar elbow fractures

2.1 ABSTRACT

Background. Surgical complications of Kirschner wire fixation of supracondylar elbow fractures are common and include infection, malunion and iatrogenic nerve injury. Defining the prevalence of these complications within a large tertiary centre offers insight into current surgical practice and avenues for the development of new techniques.

Methods. The electronic records of all patients who sustained an operatively managed supracondylar elbow fracture between 14/9/12 and 14/12/14 were evaluated with the primary outcome measures of infection, malunion and iatrogenic nerve injury. The requirement of a general anaesthetic for wire removal was a secondary outcome. Injury related complications of open fracture, neurovascular injury and compartment syndrome were also recorded. A simultaneous analysis of the outcomes of distal humerus condylar and distal radius fractures was performed.

Results. Fixation was required in 123 supracondylar fractures, 11 condylar fractures and 94 distal radius fractures. Overall infection rate was 9.7% with a major infection rate of 1.3%. No fracture resulted in a malunion that required operative intervention. One patient suffered an iatrogenic ulnar nerve injury. There was no relationship between injury mechanisms, open fracture or fracture classification, and post-operative complications.

Conclusions. Post-operative infection was the commonest surgical complication while malunion and nerve injury were rare. While the current technique of Kirschner wire fixation provided an adequate surgical construct, methods to reduce infection should be considered.

2.2 INTRODUCTION

Kirschner wires are widely employed in the fixation of displaced supracondylar fractures of the elbow. Important complications relating to surgery include infection, malunion and iatrogenic nerve injury (13-15, 40). Defining the prevalence of these complications offers opportunity for the development of new surgical techniques.

Infection is reported to be the commonest post-operative complication and relates to the percutaneous nature of Kirschner wires which are commonly left protruding from the skin to facilitate later removal. The reported prevalence of pin tract infection varies and is summarised in Table 1.1. A number of factors relating to the injury and subsequent surgery may increase the likelihood of infection. An injury that has been caused by a higher energy, is open, or has associated neurovascular compromise, may be more prone to infection (13). Such injuries may result in more challenging surgery where a number of attempts are required to place pins, increasing the risk of physeal injury and bony thermal necrosis. Malunion of supracondylar fractures is the commonest late complication and can result in a poor cosmetic outcome and the need for further surgery (46, 183). Iatrogenic nerve injury is a relatively rare complication but can potentially result in a severe functional deficit and the requirement for salvage procedures (14).

This retrospective cohort study defines the surgical complications of supracondylar elbow fracture fixation within a tertiary referral paediatric trauma centre. The primary outcomes were post-operative infection, malunion and iatrogenic nerve injury. Return to theatre for routine wire removal was the secondary outcome measure. Injury related complications of nerve damage, open fracture, vascular compromise and compartment syndrome were also defined. Further insight into the outcomes of Kirschner wire insertion in the upper limb was provided by the concurrent analysis of distal humerus condylar fractures and distal radius fractures.

2.3 METHODS

2.3.1 Permissions

Permission to perform an analysis of patient notes and radiographs was granted from the local NHS board Research and Development team. The appropriate forms were completed and permission was granted to access the Electronic Patient Records of the selected patient cohort (Appendix 1).

2.3.1 Population

The Edinburgh and Lothian's population for the period of this study was obtained from the General Register Office for Scotland (GROS)(184). The most recent national census (2011) was used to extrapolate mid-year estimates of the national population. Data on births, deaths and migration trends for the preceding year are taken into account. A full and detailed account of the methodology used by GROS to produce the annual population estimates is available on the GROS website. For this study, the mid-2012 population estimates were used to define population.

The Scottish population is most commonly analysed in region specific cohorts. Regions are based on location or by the NHS health board responsible for care. NHS Lothian health board controls a number of hospitals but only one that cares for paediatric orthopaedic patients. Therefore, the use of NHS board specific data for Lothian allows comprehensive mapping of paediatric injury and outcome for regions similar to Lothian.

2.3.2 Patient selection

The Royal Hospital for Sick Children serves a defined population. All paediatric patients under 14, and those under 16 in whom plain radiographs show incomplete physeal closure, receive inpatient and outpatient management in a single Paediatric Orthopaedic Trauma Unit (POTU). On occasion, emergency presentations erroneously attend the adult unit, which is on a separate site. All such patients under

the age of 14 are transferred to the POTU. A small number of 14-16 year olds receive treatment at the adult site, these patients were not included in the study.

Two independent logbooks of activity were used to identify patients who had suffered a supracondylar distal humerus fracture, a distal humerus condylar fracture or a distal radius fracture, that required Kirschner wire fixation.

1. ***Theatre activity logbook***. All orthopaedic procedures occur in one of two operating theatres. Each theatre has a strictly kept log of all activity which is maintained by the theatre Charge nurse.

2. ***Image intensifier activity logbook***. All procedures that require the use of intra-operative radiographs are logged by the duty Radiographer. This log is a legal requirement under the Ionising Radiation (Medical Exposure) Regulations (IRMER).

Multiplicity

In a small number of patients there were concurrent injures to the wrist and elbow which both required operative intervention. For the purposes of this study these were treated as separate injuries and procedures.

2.3.3 Radiographic evaluation

Fracture classification

All pre-operative and intra-operative radiographs were assessed by the investigator. Fractures were classified according to injury.

- *Supracondylar distal humerus fractures.* Supracondylar distal humerus fractures were classified according to the Gartland system modified to include flexion type injuries (Figure 2.1, Figure 2.2)(185). This classification is based on the relationship of the distal fracture fragment to the anterior humeral line. Gartland I fractures do not require operative treatment and were therefore not included in this study.

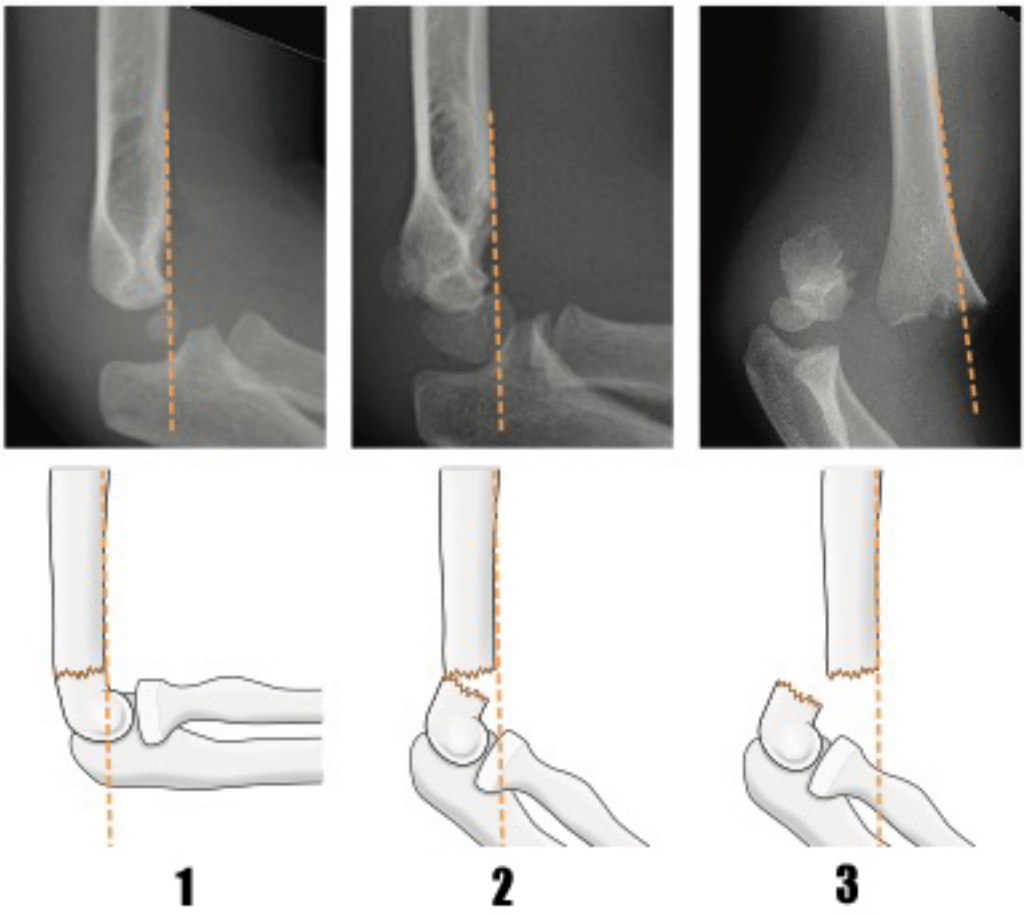

Figure 2.1: The Gartland classification of supracondylar fractures. With permission of the authors from "McRae's Orthopaedic Trauma and Emergency Fracture Management"

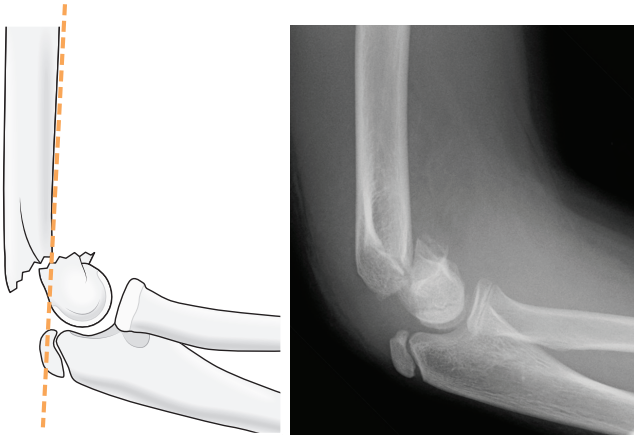

Figure 2.2: Flexion type supracondylar fracture. With permission of the authors from "McRae's Orthopaedic Trauma and Emergency Fracture Management"

- *Condylar fractures.* Those fractures affecting the medial condyle were noted as separate injures; no formal classification system was employed. Those affecting the lateral condyle were classified according to the Milch system which comments on the involvement of the articular surface (Figure 2.3)(186).

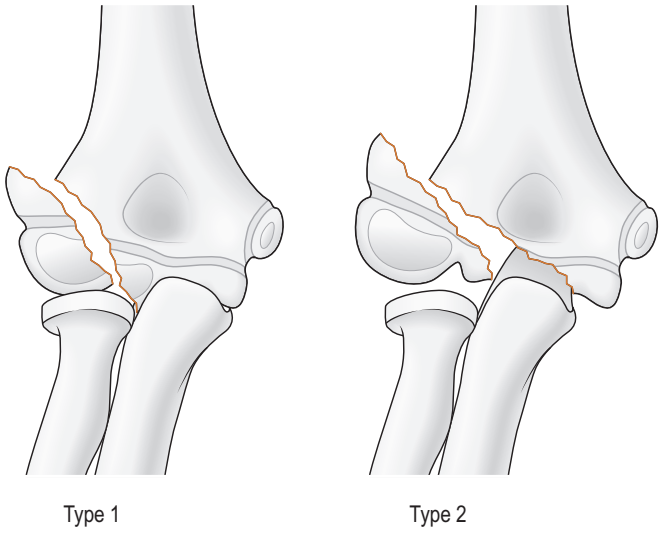

Figure 2.3: The Milch classification. With permission of the authors from "McRae's Orthopaedic Trauma and Emergency Fracture Management"

- *Distal radius fractures.* Injuries affecting the distal radius do not have a unified classification system. For this study, radiographs were first scrutinized to assess physeal involvement. If the physis was involved, the fracture was classified according to the Salter Harris system (Figure 1.3). All other fractures were termed "extra physeal". Additionally, comment was made on deformity in the sagittal plane - either dorsal or volar.

Fixation method

Fixation method was categorised by the number and configuration of the Kirschner wires.

- *Supracondylar elbow fractures.* Two or three Kirschner wires are employed in supracondylar fracture fixation. The lateral and crossed wire technique were both recorded.

- *Condylar elbow fractures.* One or two retrograde Kirschner wires were employed in the fixation of condylar fractures. Start point is defined by the injury, with the medial epicondyle for medial condyle injuries, and the lateral epicondyle for lateral condyle injuries.

- *Distal radius fractures.* One or two Kirschner wires are passed retrograde for the fixation of distal radius fractures. Fractures involving the physis require K wire fixation across the growth plate (trans-physeal). Some extra-physeal fractures were secured with wires that started proximal to the physis (infra-physeal).

2.3.4 Clinical note evaluation

NHS Lothian utilises an electronic patient record system (TRAKcare). Patients have an Electronic Patient Record (EPR) which contains all inpatient and outpatient notes and a record detailing any radiological, microbiological or pathological results. Notes were scrutinized two years post-operative to determine the complication rates.

Infection

Superficial infections were defined by cellulitis around the pin site, pus from the pin site, a positive microbiology swab, or the prescription of oral antibiotics. Deep infections were defined by admission, intravenous antibiotics and/or operative intervention. All available records of antibiotic prescription, type and dose, were recorded. Number of re-operations and procedure type were recorded in the cases of deep infection. The results of any microbiology culture and sensitivities were noted.

Malunion

The primary marker of malunion was the requirement for corrective osteotomy. The secondary marker was the presence of a clinical deformity as defined by the treating clinician, at the time of the last review. This was further described as an extension, flexion or varus deformity. Radiographic evaluation of malunion was not available. The EPR database for the local adult hospital was also checked to ensure patients

who exceeded the upper age limit for the paediatric unit had not been treated elsewhere.

Iatrogenic nerve injury

Iatrogenic nerve injuries were identified according to nerve affected, secondary procedures and functional outcome.

Secondary procedures for wire removal

Secondary procedures not related to an injury or surgical complication were recorded. The indication for wire removal under general anaesthetic was documented.

Mechanism of injury

The circumstances surrounding the fracture were categorised according to the mechanism of injury, detailed in Table 2.1.

Mechanism of injury	Criteria
Fall: Standing height	All falls from standing high, stationary or in motion
Fall: height >0.5m	Any fall from greater than standing height
Sport	Any fall during sporting activity
Stairs	Fall down 2 or more stairs
Trampoline	Those injuries involving a trampoline
Pushbike	From pushbike, skateboard, rollerblades
Non-accidental injury	Identified from Emergency department notes and confirmed on subsequent inpatient notes

Table 2.1: Mechanisms of injury

Injury complications

In order to determine complications relating to the original injury all Emergency Department and Orthopaedic notes were assessed for documentation of:

- Open injury
- Neurovascular dysfunction
- Compartment syndrome

2.3.5 Standard operating procedure

All procedures and post-operative care in the POTU follow a defined protocol. Surgery is performed within 24hrs of injury by a Senior Registrar (at least five years of orthopaedic experience) or Consultant Orthopaedic surgeon. Elbow and wrist injuries are placed in an above elbow cast post operatively, with cast and wire removal at three weeks. Wire removal occurs in a specialist plaster technician clinic without anaesthesia but the occasional the use of nitrous oxide. General anaesthesia is used for those patients who cannot tolerate removal in the clinic.

2.3.6 Data protection

All personal information was stored and only accessible on NHS Lothian computers. The information was kept in two separate spread sheets. The first contained all personal patient information with a unique anonymisation code assigned to each patient. The second spread sheet used the anonymisation code and contained all injury and procedure related information. In this way, patient personal information was kept separate from clinical information at all times.

2.3.7 Statistical analysis

Microsoft Excel 2010 (Microsoft Corp, Redmond, Washington, USA) and SPSS version 21 (SPSS, Chicago, Illinois, USA) were used to undertake the statistical analysis. The relationship between infection and each explanatory variable was examined using Fishers Exact tests (2-category variable) or a Chi square test (variables with 3 or more categories). A p-value of <0.05 was considered statistically significant. Incidence of infection was calculated as the number of fractures per 10,000 head of population per year (N/10,000/year). For the purposes of this study all incidences are quoted for the under 16 population only[1].

[1] Guidance on the choice of statistical tests and the execution of the analysis was provided by Mr Andrew D Duckworth.

2.4 RESULTS

2.4.1 Incidence and injury mechanism

The NHS Lothian population from 1st July 2012 to 31st June 2013 totalled 843,733 with 143,363 under the age of 16 years. The age distribution for the under 16 population served by NHS Lothian is shown in Figure 2.4.

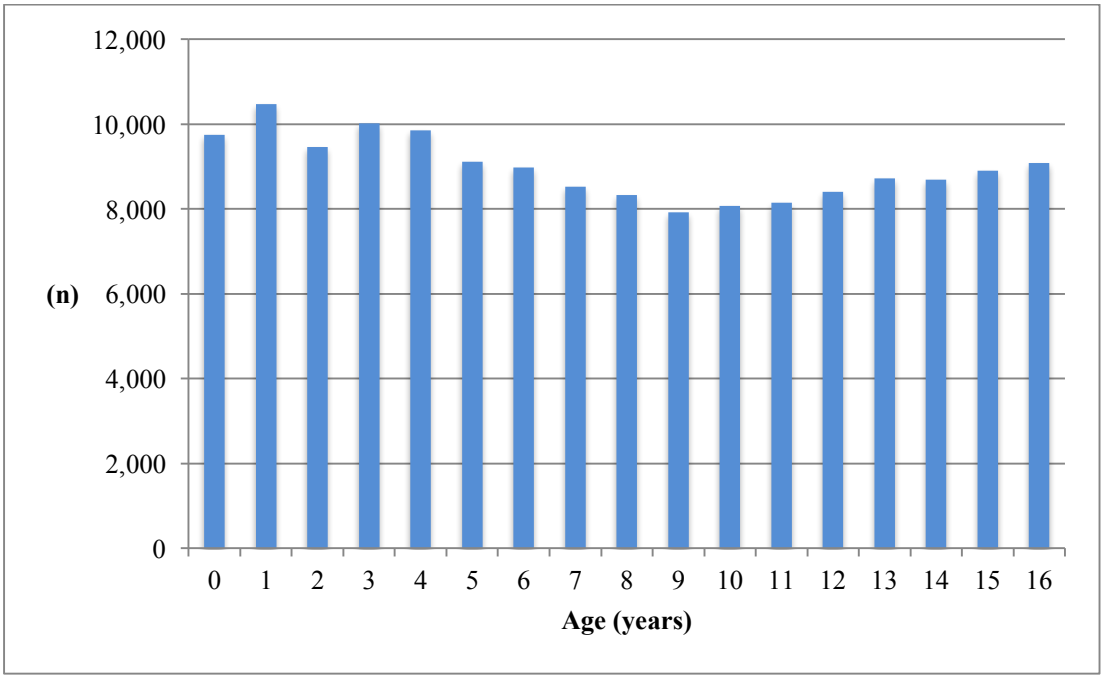

Figure 2.4: Age distribution for the population served by NHS Lothian

A total of 228 Kirschner wiring procedures (in 224 patients) were performed between 14/9/12 and 14/12/14 (27 months), giving an average of 109.4 procedures each year. Overall prevalence of injuries to the wrist and elbow that required Kirschner wire fixation was 7.6/10,000/year.

Of the 228 procedures, 134 involved the elbow compared to 94 at the wrist. Mean age at the time of surgery was 7.3 years, with a median of 7years (Interquartile range 5, range 13). The majority of surgeries were performed on males (M:F, 69:31%).

Mechanism of injury

The six different injury mechanisms are listed in Table 2.2 in descending frequency. The majority of injuries represent the various play activities enjoyed by children.

Mechanism of injury	Patient n(%)	Mean age (Yrs)	Gender (M:F,%)	Elbow fracture (%)	Wrist fracture (%)
Fall: height >0.5m	111 (49)	6.7	60:40	31.1	17.5
Fall: standing height	44 (19)	6.2	55:45	15.4	3.9
Push bike	32 (14)	9.4	69:31	3.9	10.1
Sports	20 (9)	11	85:15	1.8	7.0
Trampoline	20 (9)	6.6	45:55	7.0	1.8
NAI	1 (0.4)	13	100:0	0.0	0.4
Total	**228**	**7.4**	**69:31**	**59.2**	**40.8**

Table 2.2: Mechanism of injury and fracture frequency

Elbow fractures

A similar number of Gartland II and III fractures required fixation; flexion type injures were less common (Table 2.3). The predominant surgical technique employed two lateral wires. Crossed wires were used in four cases, one Gartland II and three Gartland III fractures.

		K-wire configuration		Number of K-wires		
Injury	Patient n (%)	Lateral n (%)	Crossed n (%)	2 wires n (%)	3 wires n (%)	Infection n (%)
Gartland II	62 (46)	61 (45)	1 (0.7)	52 (39)	10 (7.5)	6 (4.4)
Gartland III	59 (44)	56, (41)	3 (2.2)	53, (40)	6 (4.5)	7 (5.2)
Flexion type	2(1.5)	2 (1.5)	0 (0)	2(1.5)	0 (0)	0 (0)
Medial condyle	2 (1.5)	0 (0)	2 (1.5)	2 (1.5)	0 (0)	1 (0.7)
Milch 1	6 (4.5)	5 (3.7)	1 (0.7)	6 (4.5)	0 (0)	0 (0)
Milch 2	3 (2)	3 (2.2)	0 (0)	3 (2.2)	0 (0)	0 (0)
Total	**134 (100)**	**127 (94.8)**	**7 (5)**	**118 (88)**	**16 (12)**	**14 (10)**

Table 2.3: Elbow fractures by classification

Distal radius fractures

Fewer distal radius fractures required intervention over the study period (Table 2.4). In most cases, a single Kirschner wire provided adequate fixation (84 vs 10) but in only 17% of cases could the physis be avoided. Despite the predominant use of a single Kirschner wire, the incidence of infection was only slightly less than for the distal humerus (9.6% vs 10.2%).

		K-wire configuration		Number of K-wires		
Classification	**Patient n(%)**	**Trans-physeal n(%)**	**Infra-physeal n(%)**	**1 wire n(%)**	**2 wires n(%)**	**Infection n(%)**
Salter Harris I	3 (3)	3 (3.2)	0 (0)	3 (3.2)	0 (0)	0 (0)
Salter Harris II	41 (44)	41 (43.6)	0 (0)	40 (42)	1 (1.1)	5 (5.3)
Extra-physeal	50 (53)	34 (44.7)	16, (17)	41 (43)	9 (9.6)	4 (4.3)
Total	**94 (100)**	**78 (83)**	**16 (17)**	**84 (89)**	**10 (10)**	**9 (9.6)**

Table 2.4: Distal radius fractures by classification

2.4.2 Infection

There were 22 cases of infection in the 228 procedures (9.6%). The incidence was 0.73/10,000/yr. The distribution of infection across all Kirschner wire procedures and the incidence of open fractures and reductions is shown in Table 2.5.

	n	Number of K-wires (mean)	Open fracture (n= 4)	Open reduction (n=14)	Elbow: wrist (n=228)
No infection	205	1.7	3	11	120:86
All infection	**22**	**1.7**	**1**	**3**	**14:8**
Minor	19	1.7	1	3	11:8
Major	3	2	0	0	3:0

Table 2.5: Kirschner wire related infection

The details of each post-operative infection of elbow and wrist fractures are shown in Table 2.6. Positive microbiology cultures were seen in 9 of the 22 cases, with *Staphylococcus aureus* the commonest organism.

Patient	Infection	Microbiology sample	Organism cultured	Antibiotic prescribed
9	Superficial	Nil	-	N/A
29	Superficial	Nil	-	Flucloxacillin
43	Superficial	Swab	*S. aureus*	Co-amoxiclav
46	Superficial	Swab	Nil	Flucloxacillin
54	Superficial	Swab	Nil	Co-amoxiclav
62	Superficial	Swab	*S. aureus*	Co-amoxiclav
69	Superficial	Nil	-	N/A
71	Superficial	Swab	Coliforms	Co-amoxiclav
77	Superficial	Swab	Mixed anaerobes	Co-amoxiclav
85	Superficial	Swab	*S.aureus*	Co-amoxiclav
134	Superficial	Swab	Coliforms	Co-amoxiclav
146	Deep	Nil	-	IV Flucloxacillin + Clindamycin, *then* PO Co-amoxiclav
148	Superficial	Nil	-	Co-amoxiclav
163	Superficial	Nil	-	Co-amoxiclav
165	Deep	Fluid	*E.cloacae*	IV Flucloxacillin + Clindamycin *then* PO Ciprofloxacin
181	Superficial	Nil	-	Flucloxacillin
183	Superficial	Swab	Nil	Co-amoxiclav
187	Deep	Swab	*E.cloacae*	IV Piperacillin/Tazobactam *then* PO ciprofloxacin
192	Superficial	Nil	-	Co-amoxiclav
201	Superficial	Nil	-	Flucloxacillin
204	Superficial	Nil	-	N/A
219	Superficial	Swab	*S.aureus*	Co-amoxiclav

Table 2.6: Elbow and wrist Kirschner wire related infections. Deep infections are highlighted in grey. Not available (N/A), Intravenous (IV), Per oral (PO), Staphylococcus aureus (S.aureus), Enterobacter cloacae (E.cloacae).

Deep infections

There were three cases of deep infection. All arose following closed supracondylar fracture (two Gartland II and one Gartland III). An open reduction was not required in any fracture. All three cases required admission for intravenous antibiotics and at least one further procedure. Two required a single procedure for early pin removal and tract washout. One of these two cases also had a joint aspiration which demonstrated no intra-articular infection.

The other deep infection required a total of three further operative interventions. This patient presented day 21 post-operatively with signs of systemic upset. The Kirschner wires were removed but the infection persisted and two further procedures were required for debridement and washout. Intra-articular pus was evident during the third procedure. *Enterobacter cloacae* was the causative organism and was treated with intravenous flucloxacillin and clindamycin followed by oral ciprofloxacin.

Factors related to infection

No statistically significant relationship was found between any of the chosen variables, and infection. These are summarised in Table 2.7.

Variable	Test	*p* value
Age	Chi square	0.819
Gender	Fishers exact	0.291
Mode of injury	Chi square	0.822
Elbow fracture grade	Chi square	0.8
Wrist fracture grade	Chi Square	0.866
Open fracture grade	Chi square	0.172
Surgeon grade	Fisher's exact	0.342
Number of K-wires	Chi square	0.831
Configuration of K-wires	Chi square	0.859
Social deprivation	Chi square	0.233

Table 2.7: Factors related to Kirschner wire infection

2.4.3 Malunion

No patient required a corrective osteotomy. Five cases of supracondylar fracture were noted to have a deformity at the time of last review. Two patients had a varus deformity, two had an extension deformity and one a flexion deformity. All patients had been discharged from clinic for at least 18 months with no re-referral due to issues relating to the deformity.

2.4.4 Iatrogenic nerve injury

A single case of iatrogenic ulnar nerve injury occurred. The nerve was injured during the placement of a medially based wire which had been performed through an open approach. Post-operatively the patient demonstrated loss of sensation and motor function in the distribution the ulnar nerve. The injury was confirmed during an exploratory procedure three days later but required no intervention. The patient had made a full recovery by three months after surgery.

2.4.5 Secondary procedures for wire removal

Of the 228 Kirschner wire procedures, seven patients required subsequent general anaesthetic for wire removal (3%), six cases from the elbow and one from the wrist. The patients ranged from 3-12 years of age with two procedures for pin migration and five due to intolerance of outpatient removal.

2.4.6 Injury Complications

Of the 228 cases, 33 had a neurovascular complication with 34 total incidences. Only 2 patients (0.8%) required a secondary procedure. Table 2.8 details the incidence of neurovascular compromise.

Complication	n	Percentage (%)	Age in yrs (mean)	Incidence (n/10,000/yr)	Re-operation (%)
Nerve injury					
Median	10	4.4	7.8	0.3	0.0
AIN	6	2.6	4.3	0.2	0.0
Ulnar	5	2.2	9.5	0.2	0.0
Radial	6	2.6	6.3	0.2	0.4
Total	**27**	**12.3**	**7.0**	**0.9**	**0.8**
Vascular injury					
Pink, pulseless hand	4	1.8	6.8	0.1	0.0
Cold, pulseless hand	1	0.4	7.0	0.03	0.0
Total	**5**	**2.2**	**6.8**	**0.2**	**0**

Table 2.8: Nerve and vascular complications of injury

Nerve injury

Of the patients with neurological deficit, all but one was deemed by the surgical team to be a result of the initial injury. In the 27 cases of nerve palsy related to the injury, only one required exploration and neurolysis (the radial nerve was found to have become encased in callus). All others resolved spontaneously.

Vascular

Four patients presented with a pink pulseless hand, all of which resolved after fracture fixation. All fractures were of the supracondylar elbow, one grade II and three grade III. One patient presented with a cold pulseless hand due to a Gartland III fracture, which required urgent reduction in the Emergency Department to restore circulation before definitive fixation in theatre. This patient had a concurrent median nerve palsy which resolved spontaneously. No fracture resulted in vascular injury that required repair.

Compartment syndrome

One patient re-attended clinic eight weeks after fixation of a closed Gartland III supracondylar fracture with signs of a Volkmann's ischaemic contracture of the deep

flexor compartment. Surgical exploration (undertaken to facilitate lengthening of the flexor digitorum profundus tendons) demonstrated a thrombosed brachial artery but the presence of robust collateral supply to the hand. It was presumed that the patient had a compartment syndrome/ ischaemia to the deep volar compartment of the forearm. The timing of this event was unclear, as the patient had not attended the Emergency department with acute symptoms.

2.5 DISCUSSION

In this study, we defined the prevalence of complications in a large paediatric population (143,363) after percutaneous Kirschner wire fixation of supracondylar fractures of the elbow. Complications related to Kirschner wire fixation of fractures of the humeral condyles and distal radius were also defined.

2.5.1 Infection

Infection was the commonest post-operative complication, and its potential to cause lasting morbidity remains a surgical concern. In the consecutive series reported in this study, the overall infection rate was 9.6% (22 cases) with a major infection rate of 1.3% (3 cases). While this is higher than a number of the papers included in Table 1.1, the general variation between all studies is striking. The wide range of reported incidence may be attributed to surgeon-dependent variation in the definition of superficial/minor infection. Green's criteria is useful in the discrimination between minor and major infections, but is less helpful in defining the clinical features that constitute a minor infection. Some clinicians may report erythema or granulation at a pin site as infection, while others may reserve this diagnosis for the presence of pus. In our series, a superficial infection was defined as any cellulitis, discharge, or if the patient had been prescribed antibiotics at any time by any practitioner. In 4 cases there was only the suspicion of infection or a weak indication for the antibiotic prescription. These cases were included for completeness but their exclusion would lower the overall infection rate to 7.8%, which would be in agreement with a recent large study (7.9%) (15). Rather than rely on the arbitrary end point of antibiotic prescription to determine minor infection, some authors have sought a more clinically sensitive classification that describes the appearance of the pin site. Clint *et al.* proposed a simple three-point system that is based on common clinical signs (Table 2.9) (187).

Grade	Erythema	Pain	Discharge
Good	None/minimal	None	None /minimal serous
Bad	Moderate (greater than pin diameter)	On palpation or percussion of pin	Serous discharge requiring dressing changes
Ugly	Extensive (extending away from pin site)	At rest	Heavy discharge or frank pus

Table 2.9: The "Good, Bad and Ugly" pin site grading system.

This classification would allow consistent diagnosis of pin site infection. Although it is not possible to apply this system retrospectively, the delineation between erythema, with or without serous discharge would be particularly useful. By gaining an understanding of the clinical signs that trigger antibiotic prescription, greater agreement between studies could be achieved.

Defining the prevalence of major infection is somewhat simpler as the diagnosis requires admission, parenteral antibiotics or re-operation. The reporting of major infection can therefore be considered more reliable, and less vulnerable to clinical interpretation. A mean incidence of 0.8% was found in the literature included in Table 1.1, which is only slightly lower than the findings of this study (1.3%). Our figure mirrors the outcome of the largest study by Tosti *et al* which described a major rate of 1.4% in 884 cases. In the present study, the patient cohort was served by a single paediatric orthopaedic unit, where all index procedures and subsequent admission or re-operations occurred. A review of all clinical and operative records at two years post-procedure is therefore unlikely to miss any major infections and it can be assumed that our figures are comprehensive, and would translate to other areas with similar populations.

Microbiology cultures were positive in 9 of the 22 infections, with *Staphylococcus aureus* the commonest bacterium. No resistant strains were identified despite general hospital trends demonstrating an increase in the prevalence of multiply-resistant staphylococcus in wound infection (188). Three of the positive samples were non-specific growth of coliforms or anaerobes, which most likely represents

contamination. Of the major infections, two were caused by *Enterobacter* species, the other had no recorded samples. Gram-negative organisms are implicated in 6-7% of pin related infections however *Pseudomonas aeruginosa* is the more common than Enterobacter (13, 189). The cultures from our cohort of infected Kirschner wires match the preceding evidence to suggest that empirical antibiotic guidelines should focus on staphylococcus, but have appropriate cover of gram-negative organisms, particularly in major infections (188).

A number of factors could potentially be implicated in Kirschner wire related infection. Injuries that are more severe in terms of mechanism or grading, open fractures or fractures that require open reduction, are commonly suspected. We sought a correlation between a number of such variables and infection (Table 2.7). Of the nine variables examined, none were found to be related to infection, although this may represent a type II error due to the limited number of patients. Similar studies have also failed to find correlation between infection and open fractures, open reduction or surgeon grade (15, 22).

2.5.2 Malunion

No cases of malunion required surgical intervention, with only five cases of minor elbow deformity after supracondylar fracture. Any deformity was apparent on intra-operative fluoroscopy implying that a subsequent malunion was due to inadequate operative reduction rather than the development of any deformity over time due to insufficient fixation with the Kirschner wires. Two patients were noted to have a clinically apparent cubitus varus which is the commonest deformity that leads to corrective osteotomy (46). Surgery is most commonly performed for cosmetic reasons rather than a functional deficit, and it is therefore difficult to identify consistent surgical indications. Research in this area is therefore vulnerable to selection bias. Furthermore, the limited follow up period could result in the underreporting of operative procedures. Nevertheless, the available evidence suggests that the current use of Kirschner wires, and the stability of the surgical construct, is sufficient to limit malunion.

2.5.3 Iatrogenic nerve injury

The low rate of iatrogenic injury (0.4%) can be attributed to the use of laterally based pins for the majority of supracondylar fractures. Medially based wires significantly increase the risk of iatrogenic injury to the ulnar nerve, as demonstrated in this study where one of only four medially based wires resulted in a temporary nerve palsy. Such lesions are the commonest cause for referral to a specialist nerve centre (190). This example underlines the care required when inserting medially based wires and the necessity of an open approach with identification of the ulnar nerve. Interestingly Babal *et al.* suggested that laterally based pins may increase the risk of iatrogenic median nerve injury, however no such cases were demonstrated (191).

2.5.4 Secondary wire removal procedures

Kirschner wires in the paediatric population are commonly left proud of the skin to facilitate their removal in the outpatient clinic. Buried pins have previously been investigated and while they carry a lower infection rate, the requirement for a second general anaesthetic has rendered this method unpopular (26). Significant effort is therefore made to minimise the trauma of pin removal in children. Experienced plaster technicians, the employment of play technicians as a means of distraction, and the use of nitrous oxide has meant that most pins are removed without undue stress to the child. Despite these efforts, some children may still require a secondary procedure when the pin have migrated beneath the skin, the child finds initial attempts painful, or is particularly fretful. Excluding those pins removed for infection, seven patients required a second general anaesthetic. No anaesthetic related complications were reported however the potential remains, and minimising the number of secondary procedures remains desirable.

2.5.5 Injury related complications

Nerve injury

Nerve injury was the commonest complication in this cohort, with 11.8% of patients affected. This reflects the results of a large meta-analysis in 2010 that stated traumatic neurapraxia occurred in 11.3% of supracondylar fractures(33, 191). The majority of injuries affected the median and anterior interosseous nerves, as would be expected in a group that is primarily composed of supracondylar fractures. The favourable outcomes for nerve palsy demonstrated here are in agreement with a large study by Valencia et al. of 448 patients which also demonstrated that most nerve palsies will spontaneously resolve(50). Only one nerve required exploration.

Vascular injury

Vascular injury was uncommon, with 5 cases occurring in supracondylar elbow fractures. Of these, 4 presented with a "pink pulseless hand" – the brachial artery has been compressed by the fracture but the strong collateral supply to the hand remained patent – which were addressed with manipulation and wire fixation at the earliest opportunity. The sole case of a "cold pulseless hand" – where the entire supply is compromised – was treated with urgent reduction by Emergency department staff which restored normal circulation pre-operatively. No formal exploration was required in any case. The largest study assessing rates and outcomes of vascular compromise after supracondylar fractures was performed by Choi et al in 2010(192). In 1255 supracondylar fractures treated operatively over 12 years, 33 patients had an absent pulse on admission, 9 of whom also had a poorly perfused hand. As with our cohort, the majority of cases were resolved by fracture reduction and fixation, with only 4 of their cases (all in the "cold, pulseless hand" group) requiring subsequent vascular exploration and repair. There were no reported cases of iatrogenic vascular injury.

Compartment syndrome

Compartment syndrome is a rare complication of paediatric upper limb fractures and, much like vascular injury, tends to affect fractures of the supracondylar region. In 1979, the first large cohort of patients with compartment syndrome was collected by Mubarak and Carroll (193). They reported on 55 cases over a 20-year period with 22 cases occurring in the upper limb. Fractures of the distal humerus accounted for nine cases, with all but one patient diagnosed after 24 hours of symptoms, resulting in poor outcome. Ramachandran *et al.* contacted over 50 surgeons in 4 countries to seek a relationship between compartment syndrome and any delay to initial surgery. While previous research suggested that an absent pulse was a predictor of compartment syndrome, they found that a pulse was present in all 11 cases at the time of presentation (5 were described as "strong and palpable", 6 were described as "weak but palpable') (194). Only one patient in our study suffered a compartment syndrome, albeit in slightly unusual circumstances, further demonstrating the low prevalence of this complication.

2.5.6 Limitations

Although this study benefitted from a relatively large sample group, other works have collated significantly higher numbers which would reduce the risk of a type II errors in the statistical analysis (13, 14). This study was retrospective and follow up was based on note review rather than any clinical, radiographic or patient reported outcomes. Malunion in particular may be under-represented due to the method and duration of follow up. Ambiguity in the definition of minor pin site infection, coupled with the fact that some instances were initially diagnosed and treated by General Practitioners, lead to a higher than expected overall infection rate.

2.5.7 Conclusion

This study demonstrates the local prevalence of complications after Kirschner wire fixation of supracondylar fractures of the elbow and wrist. The inclusion of condylar and distal radius fractures added further insight into the potential failings of this

fixation method. Infection was a common complication while malunion and iatrogenic nerve injury were rare. This data indicates that the current standard offers adequate mechanical ability, but methods to reduce infection should be considered.

Section 3: Mechanical assessment of the Helical Nail

3.1 ABSTRACT

Background. The Helical Nail is a bioabsorbable device that has been proposed for the stabilisation of paediatric fractures. This implant would allow primary skin closure at the time of surgery and eliminate the requirement for removal procedures. Any new fixation device must have comparable mechanical properties to the current standard of fixation.

Methods. 40 simulated supracondylar sawbone fractures were stabilised with either two crossed 1.6mm Kirschner wires, or two Helical Nails in a "bi-column" technique. The constructs were assessed in rotation and posterior translation.

Results. The Helical Nail construct had comparable stiffness (0.19785Nm vs 0.16545Nm, $p = 0.2041$) and ultimate strength (3.5476N.m vs 3.8962N.m, $p = 0.4525$) to Kirschner wires against a rotational force. However, the Helical Nail construct had inferior stiffness (10.19Nm vs 18.69Nm, $p<0.001$) and ultimate strength (42.16N vs 85.44N, $p<0.001$) against posterior translation.

Conclusion. The Helical Nail is mechanically inferior to crossed Kirschner wires in the fixation of a simulated supracondylar elbow fracture.

3.2 INTRODUCTION

Kirschner wire fixation of supracondylar distal humerus fractures aims to maintain reduction and resist the deforming muscular forces, to allow callus formation and secondary bone healing. The Helical Nail has been proposed as a replacement to Kirschner wires due to the advantages of primary skin closure at the time of surgery without the requirement for removal. Mechanical comparison to the current standard is essential before considering clinical use. Current surgical techniques vary depending on the wire configuration, number and trajectory. The majority of fractures are stabilised with two wires, however, there is disagreement between clinical and laboratory research regarding the optimal wire configuration. Wire configuration is broadly categorised into one of two techniques: "lateral" wires or "crossed" wires. The lateral technique takes advantage of the subcutaneous border of the lateral condyle which has no adjacent neurovascular structures, to insert two divergent/parallel wires. The crossed technique combines the lateral approach with the addition of a medially based wire which enters the medial condyle in a retrograde fashion. This potentially offers a more stable surgical construct but comes with a risk of neurological injury due to the intimate relationship between the ulnar nerve to the medial condyle. Clinical studies have shown that the lateral technique is often sufficient but mechanical testing has found the crossed technique to be superior (57-59, 195-197). A new device could feasibly be tested against either technique, however, from a mechanical perspective comparison with the crossed technique provides the highest degree of scrutiny. If the Helical Nail is to be considered for supracondylar fracture stabilisation, it should have comparable strength in resisting rotational and extension forces to a crossed wire configuration.

3.2.1 Null hypothesis

The Helical Nail offers torsional and extension resistance comparable to Kirschner wires in the stabilisation of supracondylar elbow fractures.

3.3 METHODS

3.3.1 Saw bone preparation

40 identical humeral saw bones (Humerus, ERP 1013, Sawbones, Pacific Research laboratories, Washington, USA) were procured from a single source. The proximal portion was resected to leave a 15cm distal end. All specimens had a simulated traverse supracondylar fracture created by saw, 4cm proximal to the most distal point of the humerus, through the olecranon fossa. This method was adopted from previous mechanical studies assessing wire configuration (58, 59, 195, 198, 199).

3.3.2 Kirschner wire fixation

20 samples had fracture fixation with standard 1.6mm Kirschner wires in a crossed wire configuration. The first wire entered the medial epicondyle, traversed the fracture site in a retrograde fashion and passed through the lateral cortex. The second wire entered the lateral epicondyle, was driven retrograde across the fracture and passed through the medial cortex. Thus, a bi-cortical grip was obtained with each Kirschner wire. The entry point of each wire was pre-marked before insertion, with an acceptable exit zone of 1cm diameter also pre-marked.

3.3.3 Helical Nail fixation

20 samples had fracture fixation with the Helical Nail. The maximum length of this device is 40mm. Instead a “bilateral column” arrangement was employed - a helical nail was passed retrograde to reside in both the medial and lateral columns, with only a distal cortical grip (Figure 3.1). Insertion of the nail was performed as recommended by the manufacturer as follows:

1. **1.1mm Kirschner guidewire**. A 1.1mm Kirschner wire was passed retrograde from the medial/lateral epicondyle into the respective column to provide maintenance of the fracture reduction and to guide helical nail placement
2. **Reaming**. An implant specific reamer was passed to a depth of 40mm.

3. **Helical nail insertion**. The 2.5mm x 40mm helical nail was inserted using the implant specific insertion device using gentle taps with a small mallet.

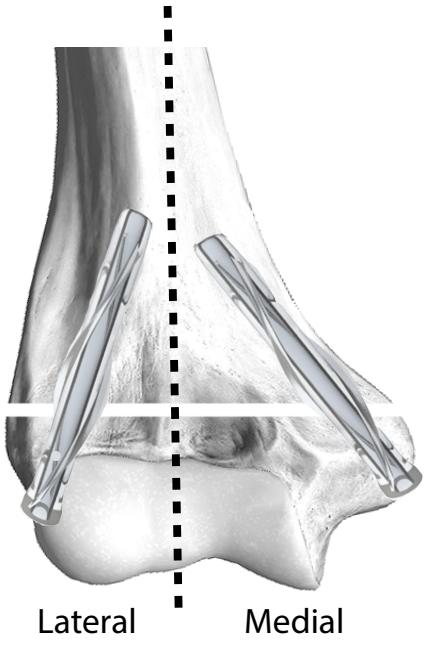

Figure 3.1: Helical Nail bi-column fixation

3.3.4 Testing apparatus

Torsional testing

10 Biotrak and 10 Kirschner wire samples were randomly selected for torsional strength testing[2]. Proximally a threaded 5mm Steinman pin was passed at right angles to the shaft, 2cm from the proximal cut. Distally, a second 5mm pin was passed along the "tie-arch" of the distal humerus.

The proximal pin was attached to the inferior arm of the mechanical testing apparatus (Zwick Roell, GMBH & Co., Germany) and the distal pin to the superior arm (Figure 3.2).

[2] All mechanical testing was performed under the supervision of Robert Wallace, Post-graduate Research Associate, Department of Orthopaedics, University of Edinburgh.

Internal rotation was applied to the fracture at a rate of 1 degree per second. Three criteria were used to compare each method of fixation:

1. The stiffness of the surgical construct against rotational deformation
2. The ultimate strength
3. The torque required to generate a "clinically relevant" deflection of 5 degrees.

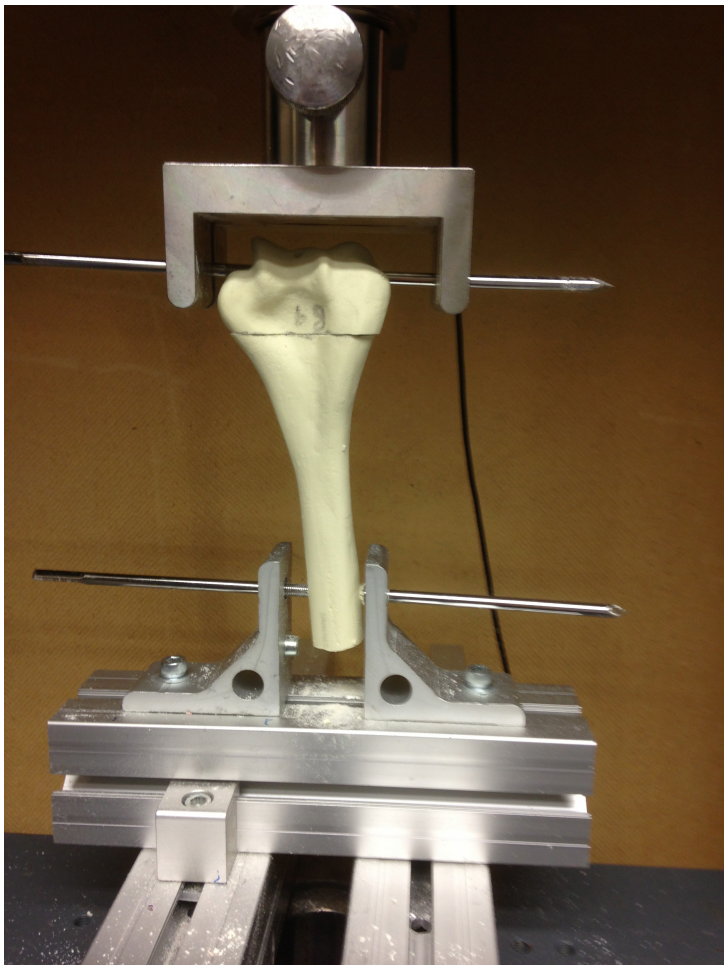

Figure 3.2: Torsional testing apparatus

Extension testing

The remaining 10 Helical Nail and 10 Kirschner wire samples were used to perform extension testing. The proximal end of the humerus was secured in a circumferential vice (Figure 3.3). The posterior aspect of the distal humerus, just proximal to the simulated fracture line was rested on a support block to ensure there was no

movement of the proximal piece. The posterior force was applied across the distal segment by the superior arm of the testing apparatus.

Deflection was applied to the fracture at a rate of 1mm per 10 seconds. Three criteria were used to compare each method of fixation.

1. The stiffness of the fixation against an extension force
2. The ultimate strength
3. The force required to generate a "clinically relevant" deflection of 3mm posterior translation.

Figure 3.3: Extension testing apparatus

3.3.5 Statistical analysis

Testing data was transferred directly to a Zwick specific program then translated to an excel spread sheet. All calculations were made using Microsoft excel and Mini tab. The data was checked for normality using the Anderson Darling equation. Differences between the control and Helical Nail groups were assessed with a two-tailed t-test.

3.4 RESULTS

The geometry of all specimens was the same, allowing for the comparison of force between samples.

3.4.1 Torsional testing

Data for both the control and Helical Nail groups were found to be normally distributed according to the Anderson Darling test (P values 0.1165 and 0.9134 respectively).

Torsional stiffness

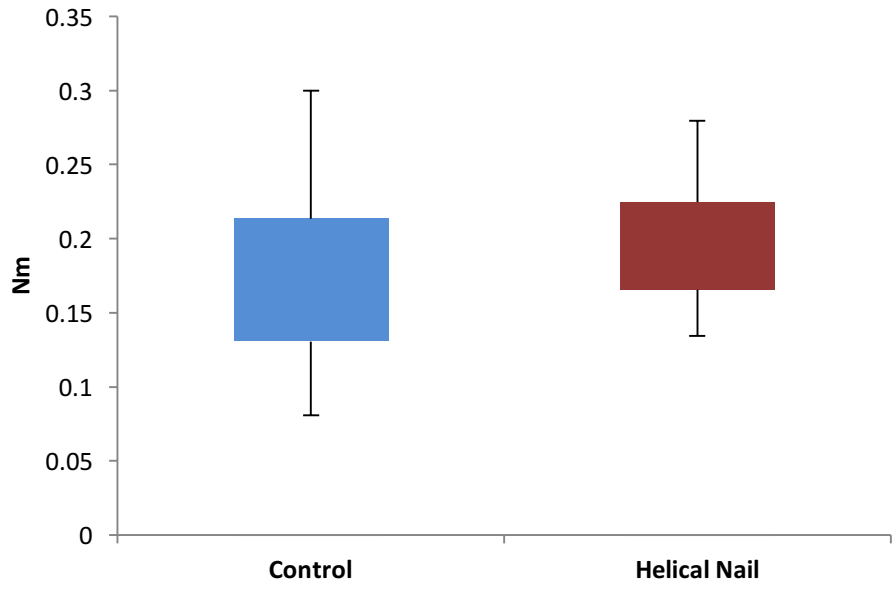

Figure 3.4: Torsional stiffness

Mean stiffness for the control group was 0.16545Nm compared to 0.19785Nm in the Helical Nail group (p value = 0.2041).

Torsional ultimate strength

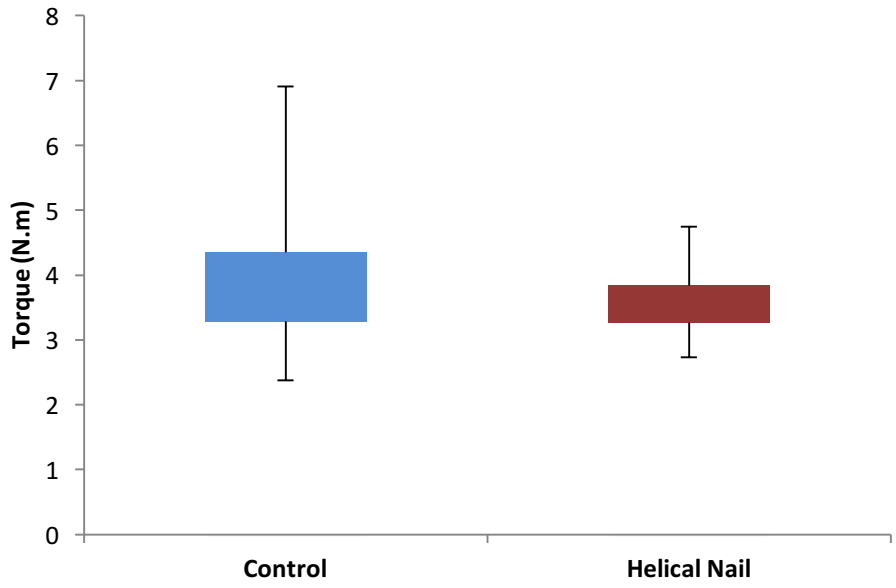

Figure 3.5: Torsional ultimate strength

Mean ultimate strength in the control group was 3.8962N.m compared to 3.5476N.m in the Helical Nail group (p = 0.4525)

Torque at 10^{o} of defection

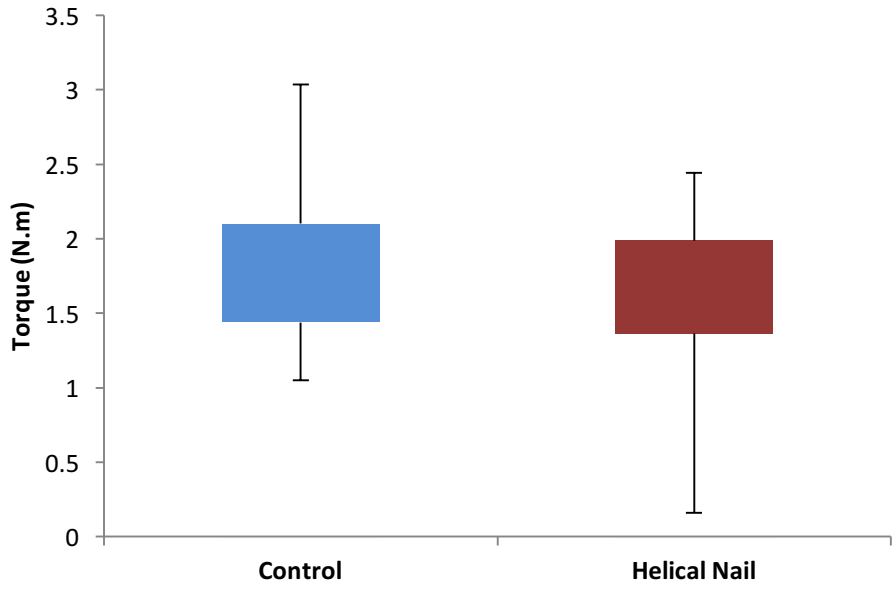

Figure 3.6: Torque at 10 degrees of deflection

Mean force to cause 10 degrees of rotational deflection was 1.7939N.m compared to 1.5520N.m in the Helical Nail group (0.4121)

3.4.2 Extension testing

All data were checked for normality using the Anderson-Darling equation. Both the control group and Helical Nail group were found to be normally distributed (P values 0.0077 and <0.0055 respectively)

Extension stiffness

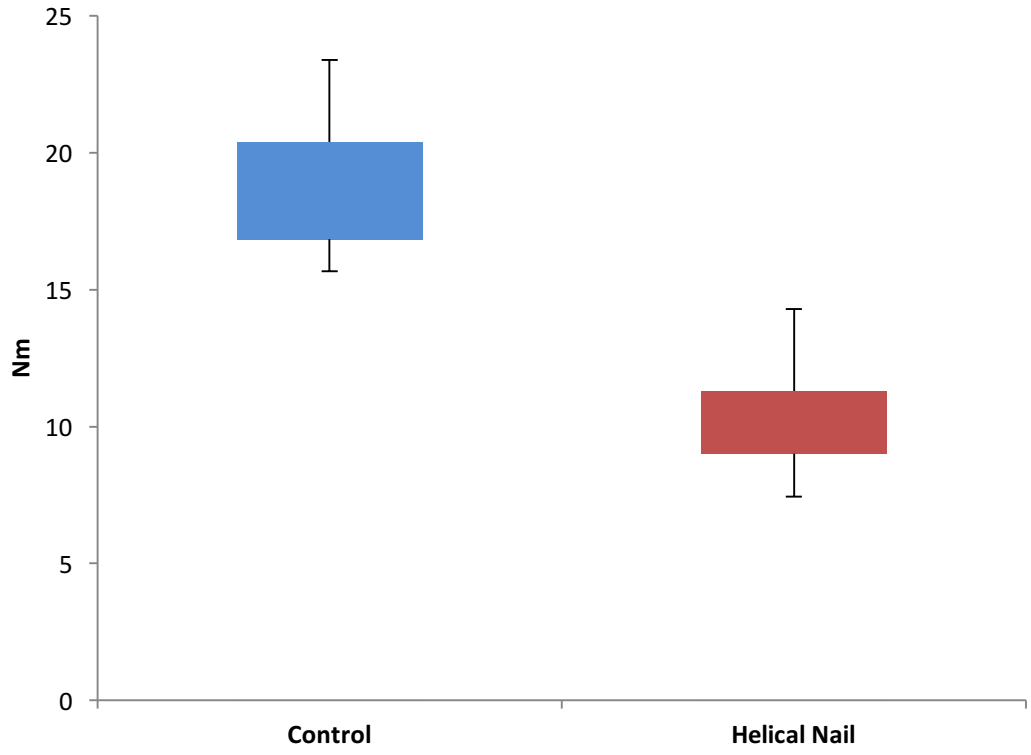

Figure 3.7: Extension stiffness

Mean stiffness for the control group was 18.69Nm compared to 10.19Nm in the Helical Nail group (p value <0.001).

Extension ultimate strength

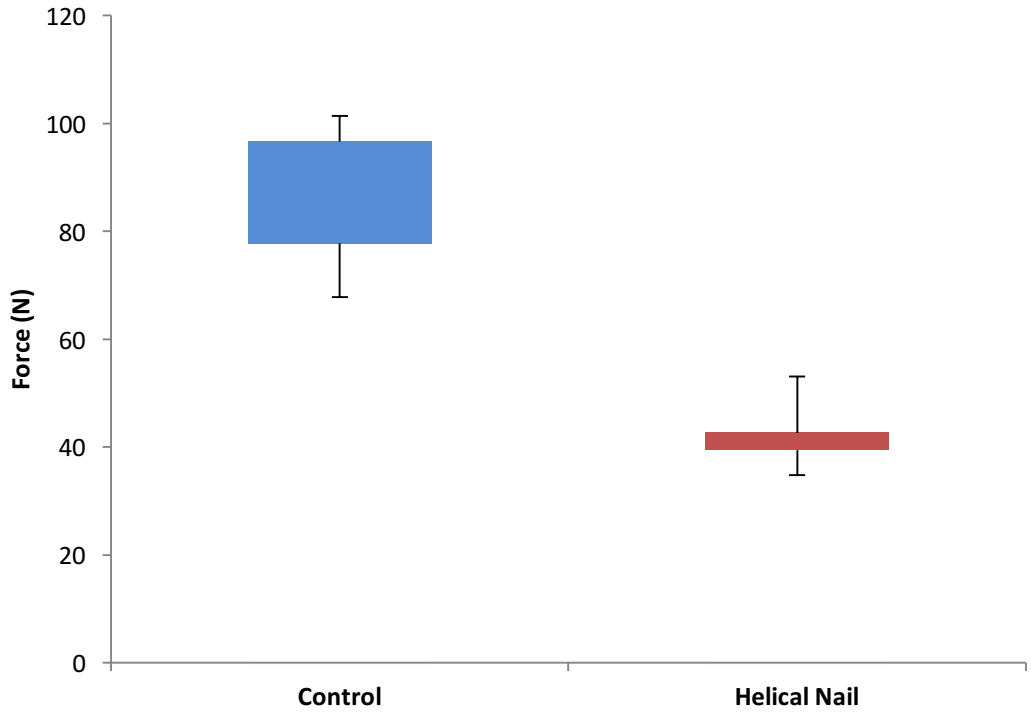

Figure 3.8: Extension ultimate strength

Mean ultimate strength for the control group was 85.4N compared to 42.16N for the Helical Nail group ($p < 0.001$).

Force at 3 mm of deflection

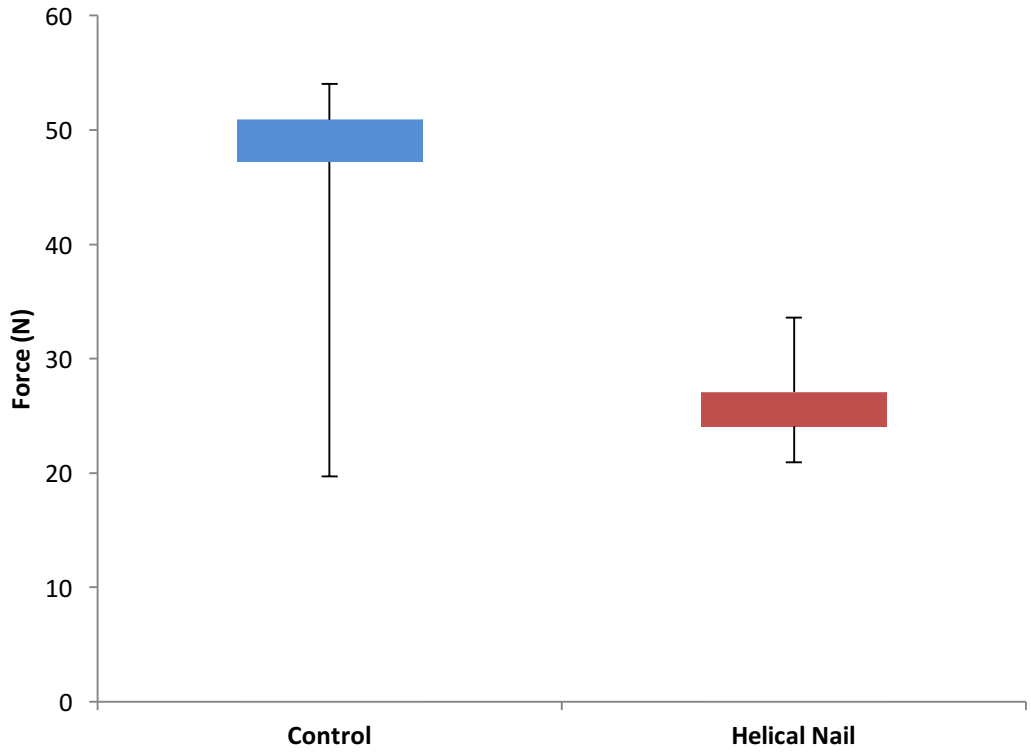

Figure 3.9: Force at 3mm of deflection

The mean force to produce a clinically relevant deflection of 3mm was 46.24N in the control group compared to 26.26N in the Helical Nail group ($p<0.001$). The box plot in Figure 3.9 shows the control group to have a skewed data spread which was due to a single outlier (control 5). The stress strain curve of said sample is shown in Figure 3.10. The initial gradient of the stress/strain curve shows a distinct change in trajectory at 4mm of deflection, something that was not evident in other samples.

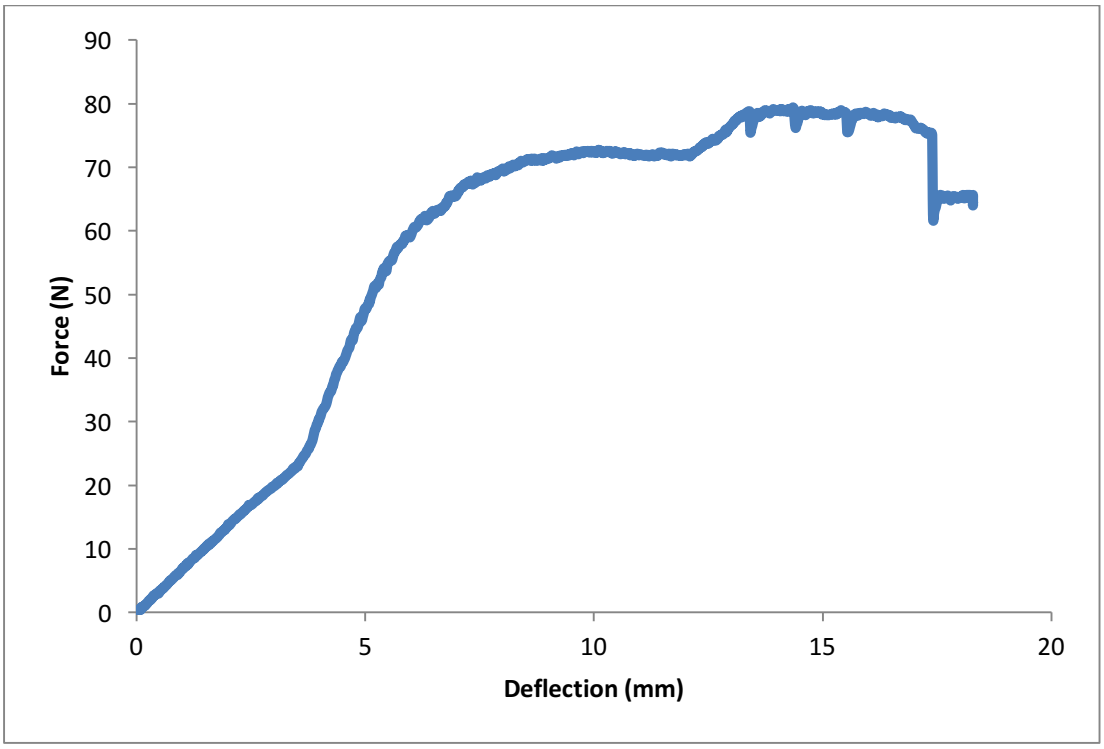

Figure 3.10: Control 5 - extension testing

3.5 DISCUSSION

3.5.1 The experimental model

The control

The introduction of a new fracture fixation device demands careful biomechanical comparison to the existing standard of practice. To investigate the Helical Nail, a testing apparatus was designed incorporating laboratory created supracondylar fractures and a custom-built rig to provide reproducible testing conditions. Cadaveric limbs were initially considered to provide a clinically realistic representation of a paediatric fracture. However, the paucity of paediatric specimens, coupled with the potentially osteoporotic nature of the elderly bones available, lead to the use of Sawbones. Although sawbones are only an approximation of real bone, adequate controls were employed. The simulated fracture was made in a uniform fashion after measurement and marking of each specimen and was based on previous works (58, 59, 195).

The method of fixation in the control group required careful consideration as uncertainty remains regarding the optimal *configuration*, *number* and *trajectory* of the Kirschner wires (Figure 3.11). As previously discussed, wire ***configuration*** is broadly categorised into two techniques ("lateral" wires or "crossed"), each with potential benefits. The ***number*** of wires required is often discussed with ongoing debate centring around the merits of a third wire, most often a medial wire used to compliment two lateral wires in unstable fractures. Finally, the ***trajectory*** of the wires, in terms of their relationship to the fracture and also to one another, is an important factor often overlooked, regardless of their number and configuration. These three factors have been extensively assessed in both the laboratory and clinical settings.

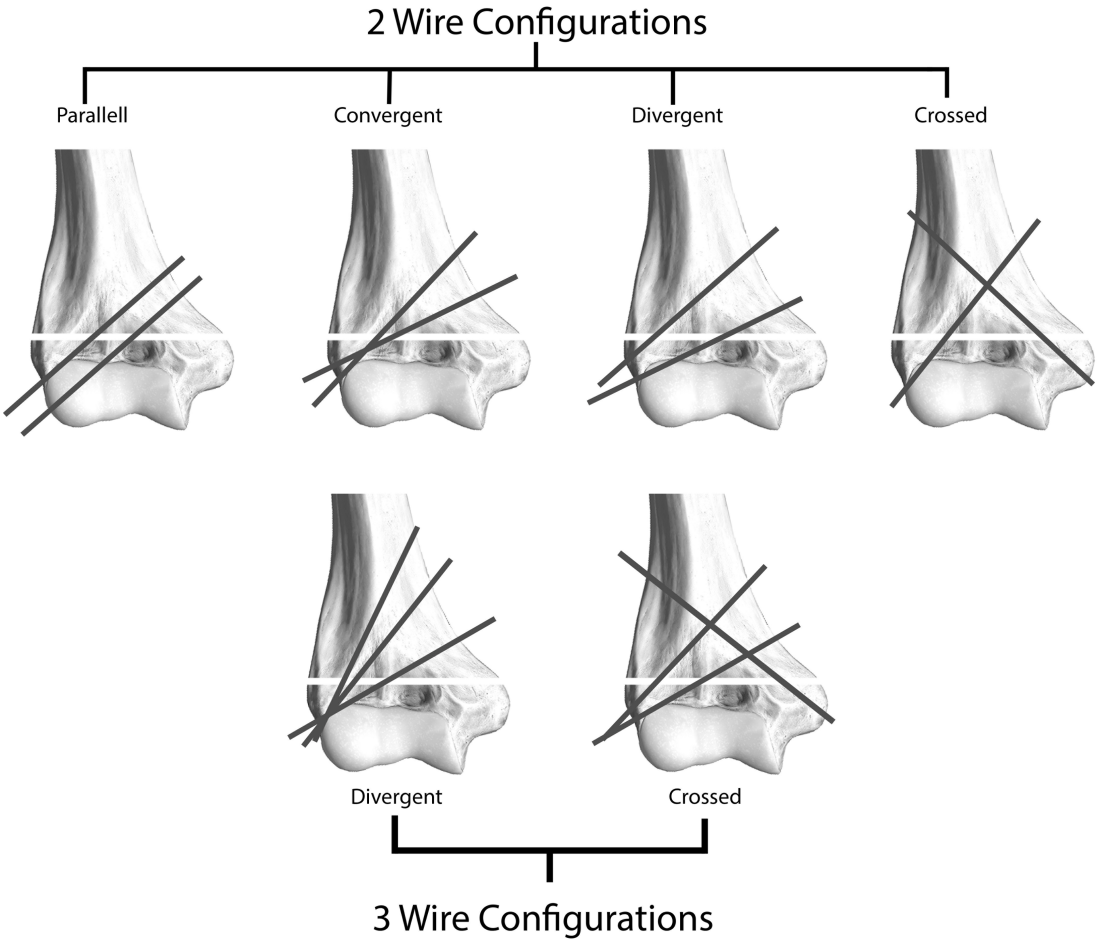

Figure 3.11: Kirschner wire configurations. The 2 wire "divergent" and "crossed" techniques are the configurations most commonly compared in biomechanical and clinical studies.

Laboratory studies have attempted to identify the strongest Kirschner wire construct for supracondylar elbow fracture stabilisation using both cadaveric and sawbone models (58, 59, 195, 198, 200). Various configurations have been assessed and tested predominantly in rotation but also in extension and varus/valgus stress (Figure 3.11). Crossed wires frequently provided superior resistance to rotational and extension forces. The *in vitro* superiority of the crossed technique was further established by *Larson et al.* They introduced a medial wedge osteotomy in sawbones to represent medial comminution and found that two crossed pins conferred stability comparable to three lateral divergent pins, with a trend towards superiority (195).

Beyond the assessment of pin number and configuration, further work has assessed the importance of pin angle and the bone/wire interface. *Hamdi et al.* looked at

various angles between two divergent lateral pins and found those pins with the greatest divergence (one proximal in line with the flare of the lateral metaphysis, the other distal crossing the fracture site at the medial edge of the coronoid fossa) offered the most stability (198). *Lamdan et al.* used finite element analysis to demonstrate the importance of the bone/wire interface (200). Under normal bone/wire interface conditions, the two-diverging lateral wire configuration offered satisfactory mechanical stability compared to crossed wires for a simple transverse fracture. When the wire/bone bonding is suboptimal, as when one or more of the lateral wires are re-drilled, the addition of a medial wire improved stability.

A number of retrospective cohort studies and randomised trials have assessed the clinical outcomes of the various wiring techniques(24, 60, 196, 201, 202). Three radiographic measurements were commonly employed to quantify post-operative displacement as a marker of construct stability: Baumann's angle, humerocapitellar angle and the intersection of the anterior humeral line with the capitelum. In all studies outcomes were comparable between crossed and lateral configurations. Laterally based wires were therefore favoured in an effort to minimise iatrogenic ulnar nerve injury, despite this being a relatively uncommon complication of medial wire placement (202).

The difference between the *in vitro* and *in vivo* studies is apparent – biomechanical analysis favours the crossed pin method while clinical evaluation shows no difference. The reasons for this are likely threefold: (1) children's bones are covered in a thick periosteum which confers significant fracture stability and this is not present in sawbone or cadaveric models, (2) the smooth, straight osteotomies in the biomechanical models lack the irregular edges of a real fracture that allow inter-digitation of fracture fragments during reduction, and increase stability, (3) clinical practice employs casting for 2-3 weeks post-surgery, limiting the force placed across the construct. From the evidence discussed, it could be suggested that while the biomechanical studies demonstrate the strongest construct, the clinical studies show which construct is 'strong enough'. However, the primary concern of this study was the assessment of the mechanical performance of the Helical Nail and the strongest

configuration that remains in clinical use was selected as the control: two crossed wires.

The Helical Nail model

The Helical Nail is a 2.5mm cannulated pin that has been proposed as a means of fracture fixation. Although the bioabsorbable properties of this implant are the primary reason for their use, additional mechanical properties may also be of benefit. Unlike a smooth Kirschner wires, the Helical Nail possesses variable pitch flutes that cause rotation of the implant during insertion, in theory providing compression. This may add resistance to deforming forces and reduce implant back out. While a PLLA polymer is less stiff than steel, the nails are thicker (2.5mm) than the Kirschner wires routinely used in clinical practice (1.6mm) thus improving their resistance to rotation and extension.

The helical nails require a different method of insertion. Their length is limited to 40mm, making a cross pin arrangement with a bicortical hold impossible. Therefore, a bi-column technique was designed and used in this study. This method limits the chance of implant crossover at the fracture site, which may be a reason for fixation failure. However, it was potentially disadvantaged by the reliance of the interface between the implant and cancellous bone, and a restricted working length.

3.5.2 Rotational testing

Although true varus angulation in the coronal plane is the predominant component of supracondylar malunion, internal rotation of the distal fragment pre-disposes to this deformity due to loss of cortical apposition. It is therefore essential that any surgical construct has the ability to resist the rotational forces inherent in supracondylar elbow fractures. Three parameters were investigated in this study to compare the rotational resistance of the two fixation methods. Stiffness was defined as the gradient of the stress (torque) strain (degree of rotation) curve. Ultimate strength was the point of construct failure. There was no statistically significant difference between the control and Helical Nails in stiffness or ultimate strength. Despite the

relative elasticity of a polymer compared to stainless steel, the implant diameter and configuration allowed the Helical Nail to provide comparable rotational resistance.

Further evaluation of the data revealed that ultimate strength occurred at a point beyond 35 degrees of rotation. While this demonstrated the absolute strength of the construct, it is less relevant to the clinical setting where the initial resistance to rotation, and thus maintenance of a bony reduction, is paramount. More useful is to calculate the torque required to produce a significant loss of reduction. However, selecting a degree of rotation that constitutes a loss of reduction is challenging, for two reasons; firstly, there is considerable disagreement within the literature as to what constitutes a loss in reduction, and secondly, the rotational component of the displacement is rarely defined. Post-operative assessment of reduction is performed primarily with plain anteroposterior (AP) and lateral radiographs. The AP film allows the measurement of varus using Baumann's angle (angle between the humeral longitudinal axis and a line drawn through the capiteller physis) with figures between 5-12 degrees arbitrarily used to define reduction loss (24, 190, 202). *Gaston et al* evaluated over 100 post-operative radiographs of grade III supracondylar fractures, measuring intra-observer variation in Baumann's angle and defining a loss of reduction as two standard deviations from the mean; a change of six degrees. The rotational component of this deformity cannot be directly measured from the plain radiographs, but can be inferred from Baumann's angle. *Camp et al* demonstrated that the degree of internal rotation is directly proportional to changes in Bauman's angle. They found that for every six degrees of varus in AP film, there has been 10 degrees of internal rotation on the axial plane (203). These figures lead us to define a loss of reduction as 10 degrees of rotation. As with the peak torque and stiffness, there was no statistically significant difference in torque to produce 10 degrees of rotation between the control and Helical Nail groups.

3.5.3 Extension testing

While varus and internal rotation are the most commonly discussed vectors in supracondylar fracture displacement, extension remains an important secondary component. Significant extension may lead to loss of triceps power and will affect

the lever arm at the humeroulnar joint. For these reasons, further testing was undertaken to assess the ability of the helical nail to resist a direct posterior force. In contrast to the rotational testing, the Helical Nails were significantly inferior with a mean stiffness and ultimate strength almost half that of the controls (18.69Nm vs 10.19Nm, 85.44N.m vs 42.16N.m). A clinically relevant value to represent a reduction loss in the sagittal plane was again sought. Sagittal displacement is recorded from lateral radiographic films and commonly cited as the failure of the anterior humeral line to intersect the ossification centre of the capitelum or a change in the lateral humerocapitellar angle of more than 5 degrees(24, 57, 190). For the purposes of this study, a posterior deflection of 3mm was chosen to represent a loss of reduction. As the results of the stiffness testing suggest, the helical nail was inferior in its initial resistance to extension, with significantly less force required to produce the 3mm deflection.

A single test subject in this cohort demonstrated an aberrant stress/strain curve. Control 5 showed a distinct change in trajectory during the plastic phase occurring at 4mm of deflection, something that was not evident in other samples. Examination of the specimen and apparatus immediately after testing did not reveal any flaws and therefore the data was not excluded. However, this sample did demonstrate some minor “cheese-wiring” at the Kirschner wires entry points and represents an initial loss of hold in the distal cortical bone. This phenomenon can occur in the clinical setting and provides a suitable explanation for these results.

3.5.4 Conclusions

This biomechanical study demonstrates the properties of the Helical Nail compared to crossed Kirschner wires for the fixation of simple supracondylar distal humerus fractures. No statistically significant difference was found when specimens were subjected to a rotational deformity. However, marked differences were seen in all parameters measured during the application of a direct posterior force. Limitations included the use of sawbones and the requirement of new implant configuration related to a restricted length. The null hypothesis could not be discounted and this

draws doubt over the devices suitability, in its current form, for use in the clinical setting.

Section 4: The effects of the Helical Nail on the ovine growth plate

4.1 ABSTRACT

Background. The Helical Nail is a bioabsorbable implant that has been proposed for transphyseal fixation of paediatric supracondylar elbow fractures. It is paramount that any device designed to replace Kirschner wires has a negligible effect on the growth plate and subsequent growth.

Methods. Two Helical Nails were inserted across the distal femoral physis in 12 immature sheep. 1.6mm Kirschner wires in the contralateral limb acted as a control. The primary outcome was femoral length six months after insertion. Micro-CT was used to assess the Helical Nails and their effect on the growth plate in terms of percentage disruption, physeal thickness, and physeal bony infiltration. Traditional histopathological techniques were used to assess for foreign body reactions.

Results. There was no difference in the length of the femora in each group. The nails disrupted 3.4% of the physeal volume. Micro-CT demonstrated that the Helical Nails lost their integrity due to intervening growth. Bony bridges were evident in both groups. Two cases of physeal tethering adjacent to a Helical Nail were identified. Physeal thickness and bony infiltration of the physis were comparable in each group. Histopathology did not reveal any significant inflammatory or foreign body reaction adjacent to the nails.

Conclusion. The Helical Nail appeared to have a negligible effect on the growth plate and did not adversely affect femoral length. The significance of physeal tethers adjacent to the helical nail is unclear.

4.2 INTRODUCTION

Closed reduction and the insertion of temporary, retrograde, transphyseal Kirschner wires is the current standard of practice in the treatment of many paediatric fractures. Their enduring success demonstrates their inert nature and negligible effect on the growth plate. However, the requirement for removal and the possibility of pin site infection provides opportunity for the development of new techniques that eliminate these drawbacks. Bioabsorbable pins that remain *in situ* and allow definitive closure of skin at the time of surgery could provide such advantages. It is paramount that any device designed to replace Kirschner wires has a negligible effect on the growth plate.

The impact of a device on the growth plate can be assessed in two broad methods (1) macroscopic assessment of the bone to determine growth and/or deformity, (2) microscopic assessment of the physis. The perspectives offered by each method combine to provide an indication of physeal health and the effects of an implant on bone development. Macroscopic assessment is most commonly performed by measurement of dissected specimens and plain radiography (172, 204). Microscopic assessment of the physis is more challenging and can be achieved in a variety of ways. Traditional analysis relied upon the techniques of histomorphometry; staining of calcified plastic-embedded bone that allowed assessment of the bone architecture, cell counting and quantification of mineralisation. The evaluation of multiple slides across a defined area provided stereographic analysis, by which the 2D results were extrapolated to provide estimates of the entire 3D region. More recently, micro-CT has emerged as an alternative. Performed at extremely high resolution, it allows assessment of an entire physis, without the need for estimation or the destructive processes required to produce microscopy slides. Areas of interest can be assessed and examined in multiple planes to identify bony infiltration of the physis and any resultant change in physeal shape. The terminology surrounding the description of these changes is somewhat unclear with terms such as bony bridges, bony bars and

physeal tethers seemingly interchangeable. For the purpose of this study, the following definitions are used to describe bony invasion of the growth plate:

- ***Bony bridge***: radiological evidence of osseous material that has fully traversed the growth plate *without* a change in expected physeal morphology.
- ***Physeal tether***: radiological evidence of osseous material that has traversed the growth plate *with* a change in expected physeal morphology

Beyond the identification of bony bridges and tethers, Micro-CT allows the accurate measurement of the ***percentage area*** destroyed by an implant, whilst simultaneously assessing other surrogate markers of physeal health:

- ***Growth plate thickness***
- ***Volume of bone infiltration into the physis*** commonly termed Bone Volume Fraction (BVF)

In the case of a bioabsorbable implant such as the Helical Nail, histopathological assessment is also necessary to identify any signs of a foreign body reaction. Only after the measurement of limb growth, quantification of physeal damage and histopathological identification of any foreign body reactions, can assertions be made as to the effects of the Helical Nail and its potential for human use.

Null hypothesis

The Biotrak Helical Nail causes greater growth plate damage and a resultant leg length discrepancy compared to traditional Kirschner wires.

4.3 ANIMALS AND METHODS

4.3.1 Development of the animal model

In order to choose the correct surgical site and optimise the procedure, the limbs of two sheep were dissected examined to allow a gross visual assessment of the bones and the various growth plates. Growth plates at the hip and shoulder were not suitable due to difficult surgical access, while those of the wrist or ankle would be at high risk of infection due to their frequent immersion in farmyard waste. The elbow joint was explored but demonstrated a very pronounced trochlea with small medial and lateral columns that would not be of sufficient size to accommodate the Helical Nail without almost complete disruption of the growth plate. The distal femur was chosen due to sufficient size, relative cleanliness and ease of access. The hind legs of the second sheep were then used to develop an appropriate surgical exposure and to familiarise the investigator with the Helical Nail insertion technique. Various incisions were attempted including, midline, para-median and direct lateral/medal. Two 5cm incisions, one lateral to expose the lateral condyle, and one medial to access to the medial condyle, were chosen. These were remote from the neurovascular bundle running down the posterior aspect of the knee. After placement of Kirschner wires in one limb and the Helical Nail in the second, the limbs were dissected and inspected for pin position and growth plate involvement.

4.3.2 Ovine model

A Home Office Personal License (PPL 70/25524) was obtained with work performed under an existing Project License (PPL 60/4052, amendment18).

Thirteen Scottish Blackface neutered male sheep of 6-7 months of age and weighing 34-37kg were studied. Each animal would act as its own control with one hind limb subjected to the novel fixation device and the other standard Kirschner wires. The animals were acclimatised to the research facility environment for two months before testing. All animals were inspected by a University of Edinburgh Veterinary surgeon, and then observed in specialist housing for 2 weeks before surgery. Food was

withheld for 24hrs, with clear fluids permitted until 4 hours pre-operatively. General anaesthesia was induced with intravenous Etomidate (Hypromidate, Janssen-Cilag, Saundeton, Buckinghamshire UK) 0.5 mg/kg and Midazolam (Hyponovel; Roche, Welwyn Garden City; UK) 0.5mg/kg. A cuffed endotracheal tube was inserted and intermittent positive pressure ventilation was instituted using a mechanical ventilator (Manley Pulmovent MPP; Harlow, Essex, UK). Inhalation of halothane (Rhodia Organique, Bristol) was used to maintain anaesthesia after induction. Throughout anaesthesia, heart rate and CO_2 were continuously monitored. A single dose of intravenous antibiotics was administered 20 minutes before commencing the procedure.

Surgical technique

Each sheep was positioned supine on an adjustable operating table and placed in 20^o of Trendelenburg tilt to move the abdomen away from the hind limbs. The sheep was carefully secured with padded straps to the forelimbs before the hind limbs were shaven, prepared with Betadine and draped. A lateral incision of 5cm was made in line with the distal femur, extending proximally from the lateral condyle. Soft tissue was dissected and diathermy was used to achieve haemostasis. The fascia lata was split and the vastus lateralis muscle was divided in line with its fibres to reveal the lateral aspect of the distal femur. Attention was then turned to the medial side with a 5cm incision made from the level of the knee joint proximally in line with the midpoint of the femur. Soft tissue was dissected bluntly and muscle divided to expose the medial femur. The femur was carefully palpated thorough both incisions simultaneously to aid proprioception before wire placement. One of two implant types were then inserted. For control limbs, two 1.6mm Kirschner wire were passed retrograde, one from the medial condyle, across the growth plate and through the opposing cortex, the other from the lateral condyle, through the growth plate then the opposing cortex. Position was confirmed by palpation of both the wire entry and exit points followed by plain radiography in both anteroposterior and lateral projections. These pins were then removed. For the Helical Nail limbs, identical incisions were made and the same process was used for the insertion of two 1.1mm Kirschner wires. These were checked on anteroposterior and lateral radiographs before the passage of

a proprietary reamer to a depth of 45mm. The reamer was removed and a cannulated 2.5 x 40mm Helical Nail was tapped into place with a small mallet. The 1.1mm Kirschner wires were removed. In all sheep, a transverse 1.6mm Kirschner wire was placed proximal to the growth plate, to provide a reference of growth for subsequent radiographs. The ends were cut short and this wire remained in situ.

The wounds were lavaged then closed in layers with 2-0 braided absorbable sutures followed by 1-0 nylon monofilament to skin. No dressings were required and the sheep was recovered under the supervision for 4 hours. The sheep remained indoors until suture removal at day 12 after operation, and were then released into a protected field. Six months after implant insertion, the sheep were euthanized with a single injection of phenobarbital 60mg/kg. The hind legs were removed and the femurs were dissected free.

4.3.3 Length assessment with plain radiography

The femurs were measured from the tip of the greater trochanter to the most distal part of the medial condyle. Plain lateral radiographs were then taken of the distal femur to include the horizontal reference wire placed at the time of surgery. The intra-operative and six month radiographs were then assessed with measurements taken from the reference wire to the most distal point of the femur (Figure 4.1).

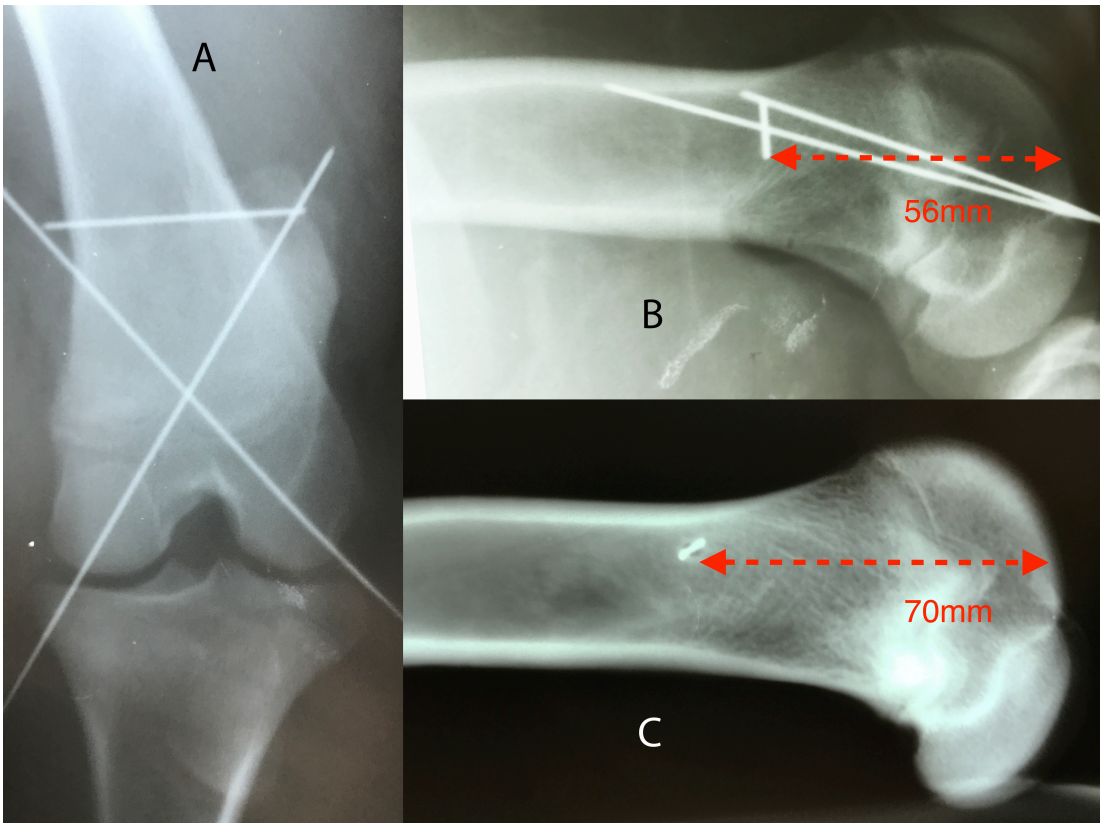

Figure 4.1: Growth measurement reference wire. (A) Intra-operative anteroposterior radiograph demonstrating the transverse reference wire in sample S11. The crossed wires are the 1.1mm guidewires required for the placement of a Helical Nail. (B) Intra-operative lateral radiograph with the reference wire proximal to the physis, red line denotes length measurement. (C) 6 month lateral radiograph of the same femur. The red dotted lines denotes the length measurements.

4.3.4 Micro-Computerised Tomography

The femurs were stored in a freezer at -20 degrees on the day of euthanasia. Subsequently the femurs were cut to leave a 5cm distal portion compatible with the micro-CT scanner.

On the day of scanning, the frozen samples were placed on a 5cm brass baseplate and covered in a 3mm layer of foam to reduce scatter. The samples were then analysed using Micro-CT (Skyscan 1172, Brussels, Belgium). The scans were composed of six parts which were reconstructed using NRecon (version 1.7.1.0, Skyscan,

Belgium), and then formatted into both axial and sagittal datasets, using Dataviewer (version 1.5.2.4, Skyscan, Belgium).

Micro-CT analysis part 1: Qualitative assessment

The reconstructed scans were scrutinized for abnormalities in the growth plate using CTvol (version 1.13, Skyscan, Belgium). Complete visualisation of the growth plate was achieved through the manipulation of the images in the coronal, sagittal and axial planes. This allowed a full appreciation of the pin trajectory and the surrounding growth plate. Comment was made on the shape of the Helical Nails (warped or unchanged), the absence or presence (and number) of bony bars, and the occurrence of any physeal tethering resulting in a change in growth plate morphology.

Micro-CT analysis part 2: Quantitative assessment

A sagittal dataset was opened using CTAn (version 1.13, Skyscan, Belgium). The physis was outlined with a 1mm border on sequential CT slices. The adaptive interpolation function was used to produce a 3D model which provided the Physeal Volume (PV) (Figure 4.3,Figure 4.2).

The ***percentage of the growth plate disrupted*** by the Helical Nails was then calculated based on the Physeal Volume. The volume of the physis disrupted by the Helical Nail was calculated and termed Nail Volume (NV). Growth plate disruption was calculated (NV/PV%).

The ***thickness of the growth plate*** was established using a series of sequential measurements from the sagittal dataset. The physis was measured for each sample by taking 3 separate measurements in a slice, and repeating this process every 30 slices (1mm) for the entire width of the sample. The mean thickness for each slice was calculated followed by the mean thickness for the sample.

Finally, the ***volume of bone infiltration*** of the cartilaginous growth plate was measured (BVF). The images were assessed using the Binary selection tool which allows the brightness or "threshold' of the images to be set, before morphometric

analysis. Two thresholds were used; the automatic function offered by the program, and another defined by the user to best define mineralised bone. A 3D analysis was then performed using the Morphometry function which calculates the volume of bone within the physis, termed Bone Volume (BV). The Bone Volume Fraction was then calculated (BV/PV%).

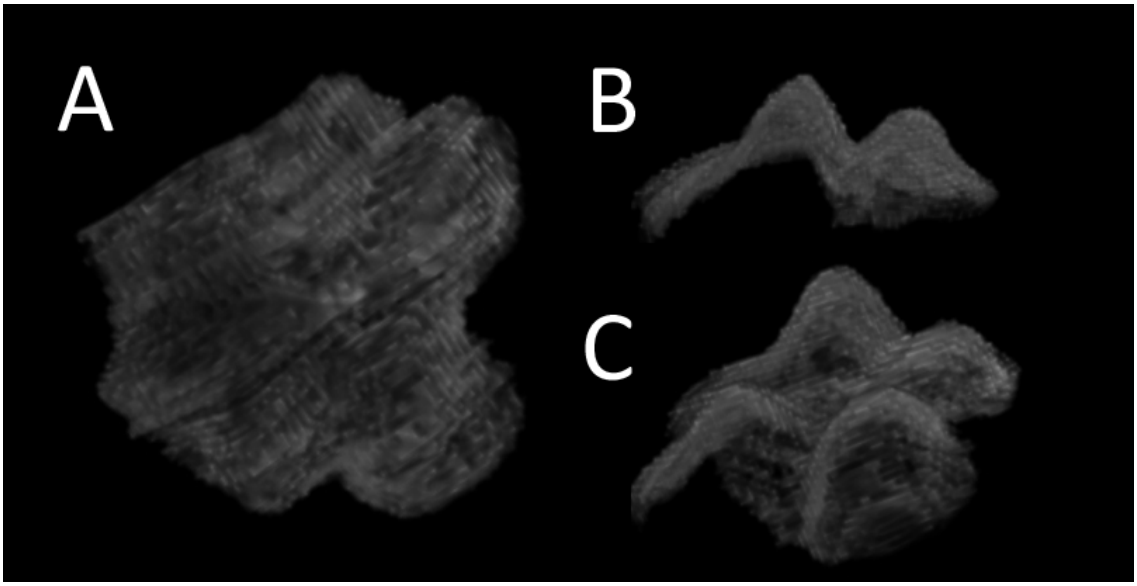

Figure 4.2: 3D reconstruction of an ovine distal femur physis. (A) axial view, (B) lateral view, (C) oblique view.

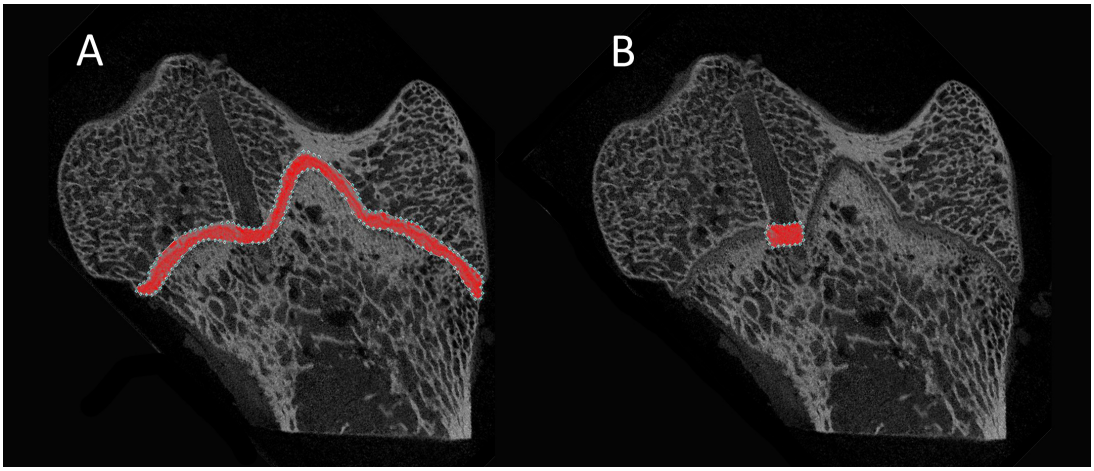

Figure 4.3: Defining the physis and Helical Nail invasion. (A) shows the outline taken of the growth plate on a typical micro-CT slice. (B) shows the area of growth plate disrupted by a Helical Nail.

4.3.5 Histopathological assessment

After micro-CT scanning, the distal femora were resected to produce samples of a suitable size for histopathological assessment. Initially, 8mm core biopsies were taken using a high speed drill. The samples were held in a custom 3D printed jig which allowed cutting to occur while the sample was submerged in water to limit thermal damage. This technique was subsequently modified to improve sampling of the Helical Nails, by the use of sequential cutting with a slow speed, irrigated, circular diamond tipped saw. The samples were then fixed in 4% formaldehyde for 48hrs before undergoing decalcification in EDTA (4-6 weeks). The blocks were embedded in paraffin and 4 micron sections were made until a portion of the nail crossing the growth plate was visible. Sections were stained using Haematoxylin and eosin. Histological analysis was performed under light magnification[3].

4.3.6 Statistical analysis

Microsoft Excel 2010 (Microsoft Corp, Redmond, Washington) Minitab version 1.2.0 and SPSS version 21 (SPSS, Chicago, Illinois) were used to undertake the statistical analysis. Comparison between the test and control subjects was performed using a paired student *t*-test. The relationship between femoral length and bony bridge, physeal tethering and growth plate disruption was examined using Fishers Exact tests (2-category variable). A *p*-value of <0.05 was considered statistically significant.

[3] Slide preparation was performed in the Shared Universities Research Facilities (SURF) laboratory by lead technician Melanie McCann. Slide analysis was performed by Dr Andrew Wood, Senior registrar in Clinical Pathology.

4.4 RESULTS

4.4.1 Helical Nail insertion

General complications

In accordance with the Animal Licence, the sheep were regularly inspected by the University of Edinburgh animal technicians to ensure their wellbeing. There were no cases of surgical site infection, nor were there any problems with the operated knees. One animal demonstrated a non-specific limp approximately 3 months post-operatively, however examination did not reveal any issues and symptoms resolved within 24 hours.

Implant related complications

Twelve animals were originally planned for the study; a thirteenth animal was required due to single case of implant failure at the time of surgery. The single case of implant failure was encountered in animal six. The 1.1mm Kirschner wire had developed a kink during insertion, which affected the passage of the reamer and caused the flutes to blunt (Figure 4.4). The case was not completed as the pin tracts could not be adequately prepared.

Figure 4.4: The Helical Nail reamer. On the left of the picture is an intact reamer with sharp flutes and a pointed tip. On the right is a blunted device after attempted reaming over a kinked Kirschner wire.

4.4.2 Femoral length

The length of the 12 pairs of femora were measured, from the tip of the greater trochanter to the most distal aspect of the lateral condyle, with the results shown in Figure 4.5. There was no statistical difference in the mean femoral length at six months between the control and Helical Nail groups (185mm, ± SD 5.9 vs 186mm, ± SD 5.8; p=0.8).

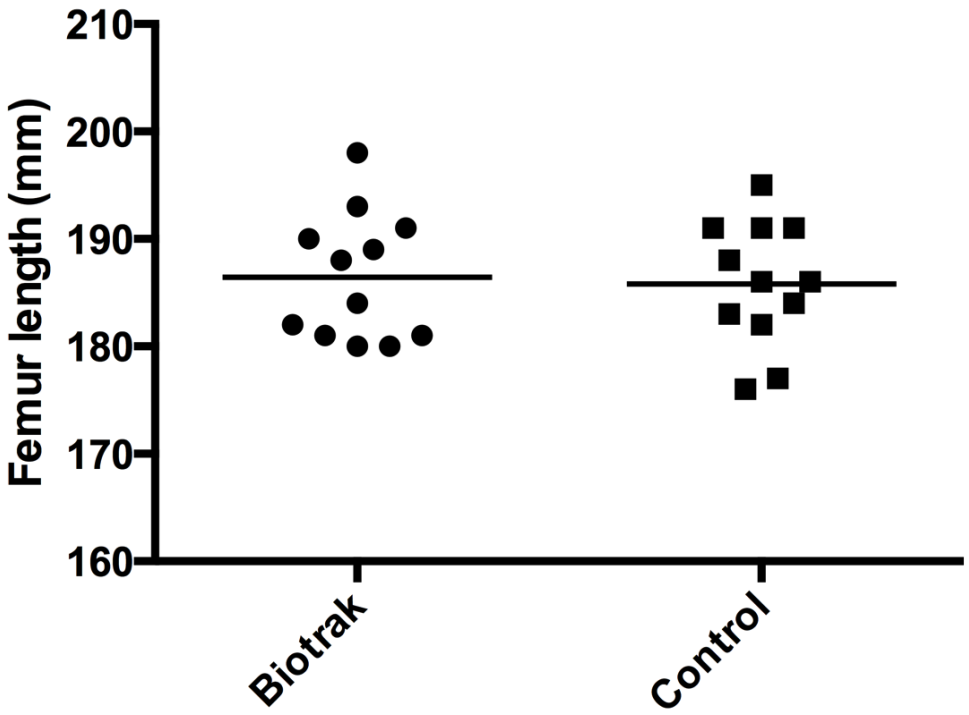

Figure 4.5: Femoral length six months after Helical Nail insertion. The mean is denoted by the solid horizontal line.

An assessment of growth over six months since surgery was calculated radiographically. Plain lateral radiographs, taken at the time of surgery, and at the time of euthanasia, were compared for bone length distal to the reference wire (Figure 4.6). There was no statistically significant difference in the change in femoral length of growth distal to the reference wire over 6 months (Control: mean 14.8mm, ± SD 4.9, Biotrak mean 13.9mm ± SD 4.1, p=0.6)

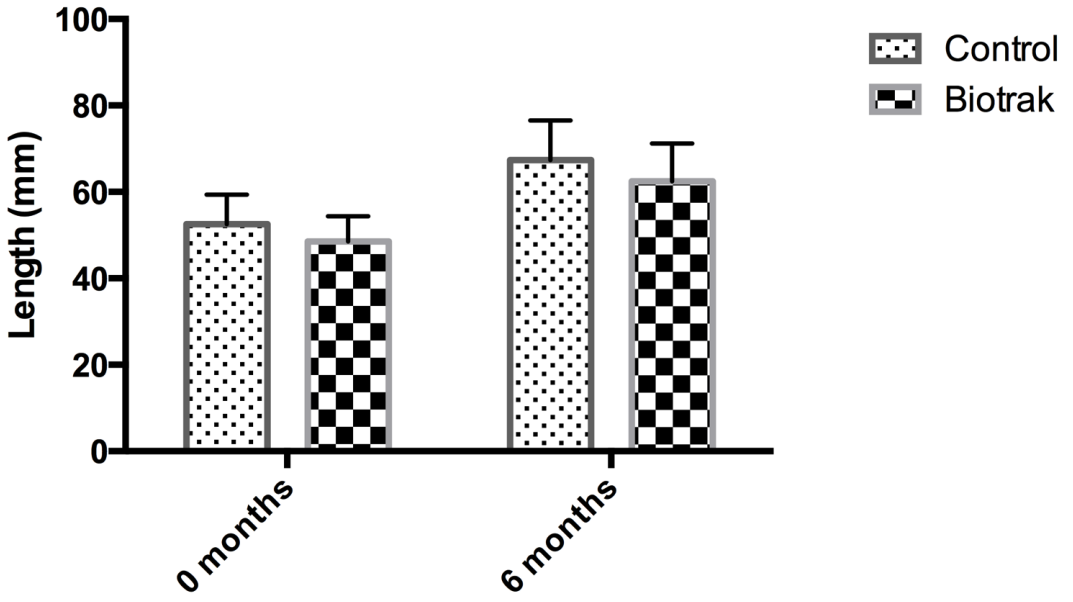

Figure 4.6: Mean change in femoral length over 6 months.

4.4.3 Micro- CT analysis part 1: Qualitative assessment

Of the 24 distal femurs, three scans were disrupted due to accidental movement of the sample during scanning: both scans for sheep 3 and the control for sheep 7. This left 11 samples with Helical Nails and 10 with Kirschner wires. Qualitative analysis was performed on all available scans, while quantitative analysis was only performed on those samples with a matched control.

Of the 22 Helical Nails inserted into 11 sheep femora, 21 crossed the growth plate (animal 7 had a Helical Nail with a start point proximal to the growth plate). Assessment of the Helical Nails was undertaken in three fields of view; coronal, sagittal and axial. The results are shown in Table 4.1.

Helical Nail morphology

The majority of the Helical Nails had undergone a change in shape (17/21). Those nails that encountered the physis at a more oblique angle were the most misshapen (Figure 4.7).

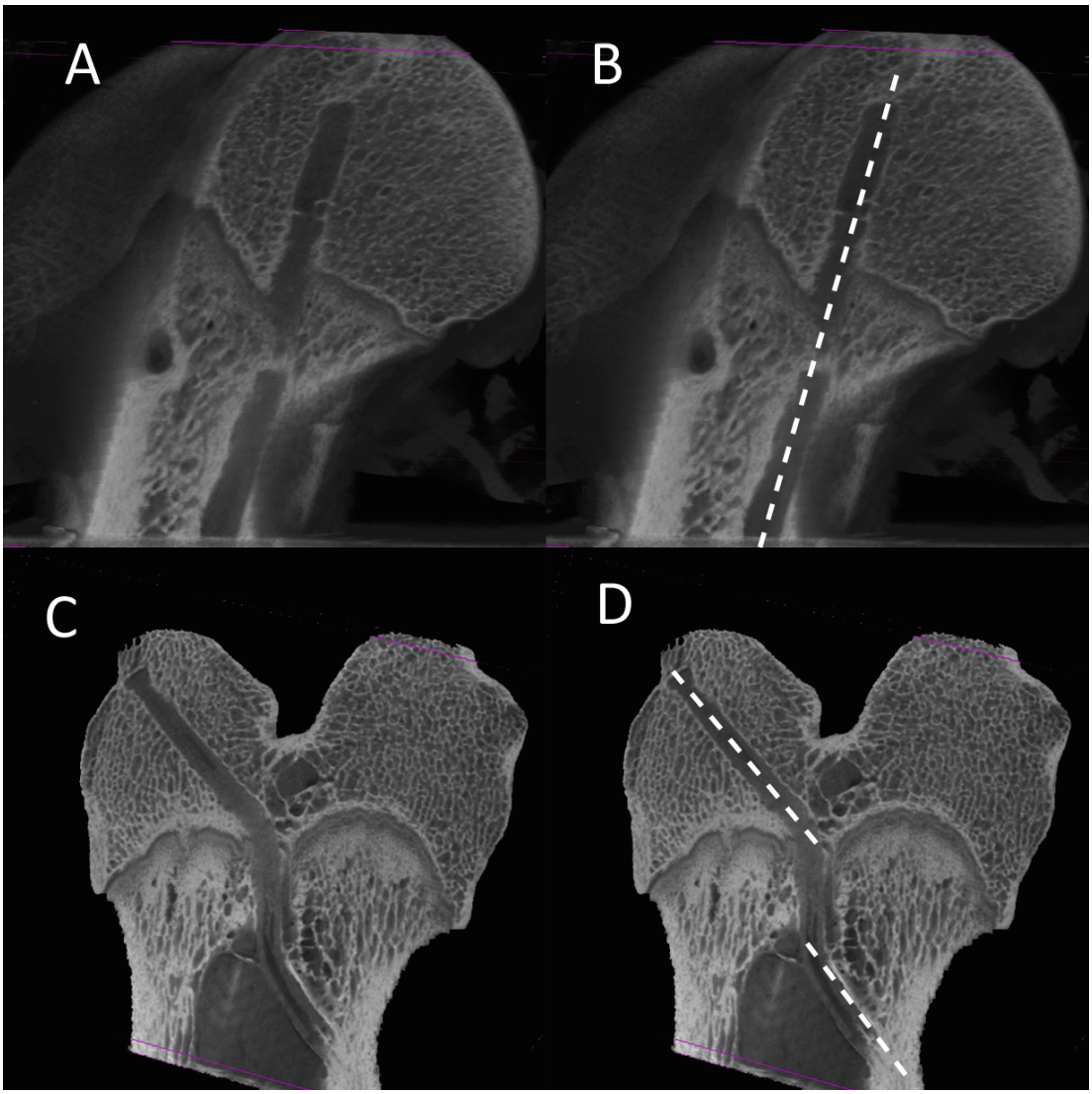

Figure 4.7: Helical Nails at 6 months. (A,B) shows a nail with a largely unchanged trajectory in a single plane. (C) shows a warped nail in a different plane, (D) demonstrates that the two oblique portions remain parallel and in line with the original trajectory while the portion at the growth plate has been "dragged" during growth.

Bony bridges

Bony bridging was seen in samples from both groups. 12 bony bridges in seven specimens occurred in the control group, compared to seven in six specimens from the Biotrak group (Figure 4.8, Figure 4.9). In the control group, all bridges occurred at the site of growth plate injury generated by the Kirschner. In the Helical Nail group the bony bridge was seen adjacent to the pin.

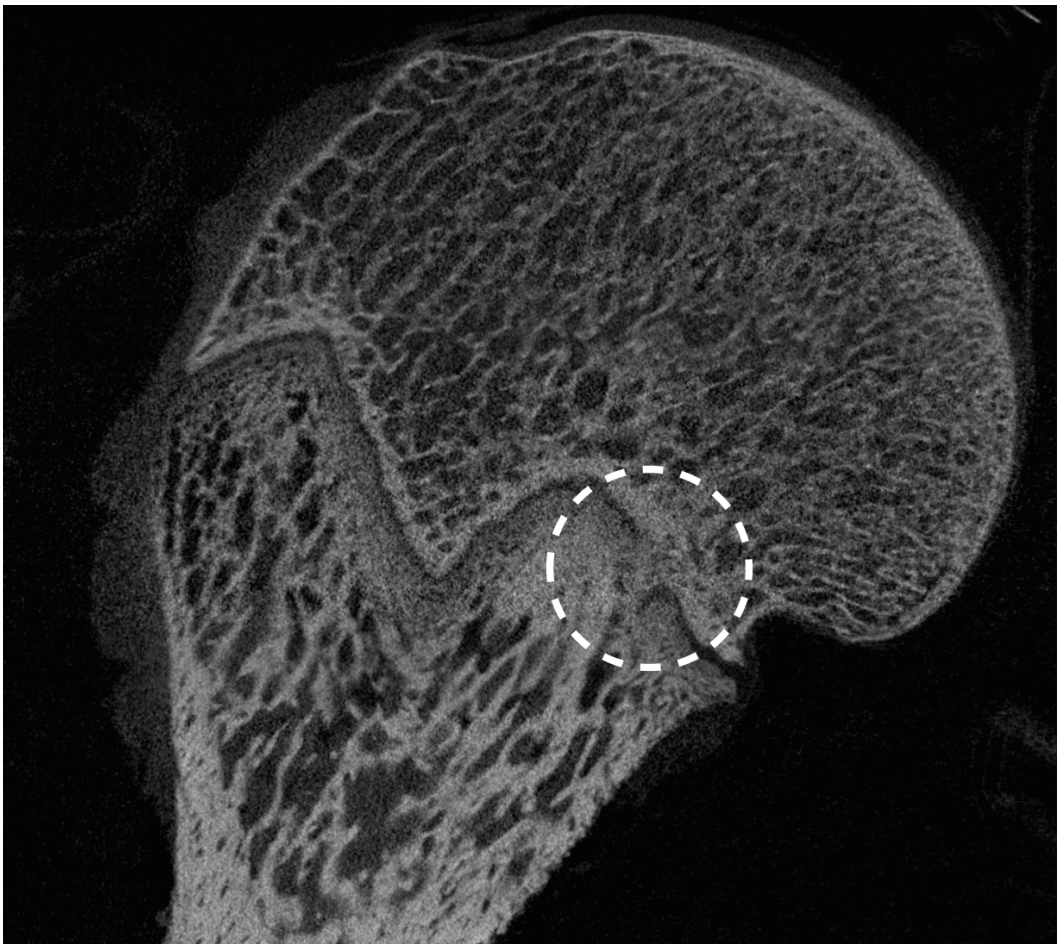

Figure 4.8: Bony bridge. Sagittal Micro-CT image demonstrating bone traversing the physis at the site of growth plate injury caused by the single passage of a 1.6mm Kirschner wire six months previously.

	Number of samples	Number of nails	Warped nails	Bony bridge	Physeal tethering
Biotrak	11	21	17	7	2
Control	10	N/A	N/A	12	0

Table 4.1: Micro-CT qualitative assessment

Figure 4.9: Bony bridge adjacent to a Helical Nail. White arrows show two Helical Nails.

Change to the morphology of the growth plate due to physeal tethering was only seen in the Helical Nail group and was associated with one Helical Nail in 3 different specimens (14%)(Figure 4.10).

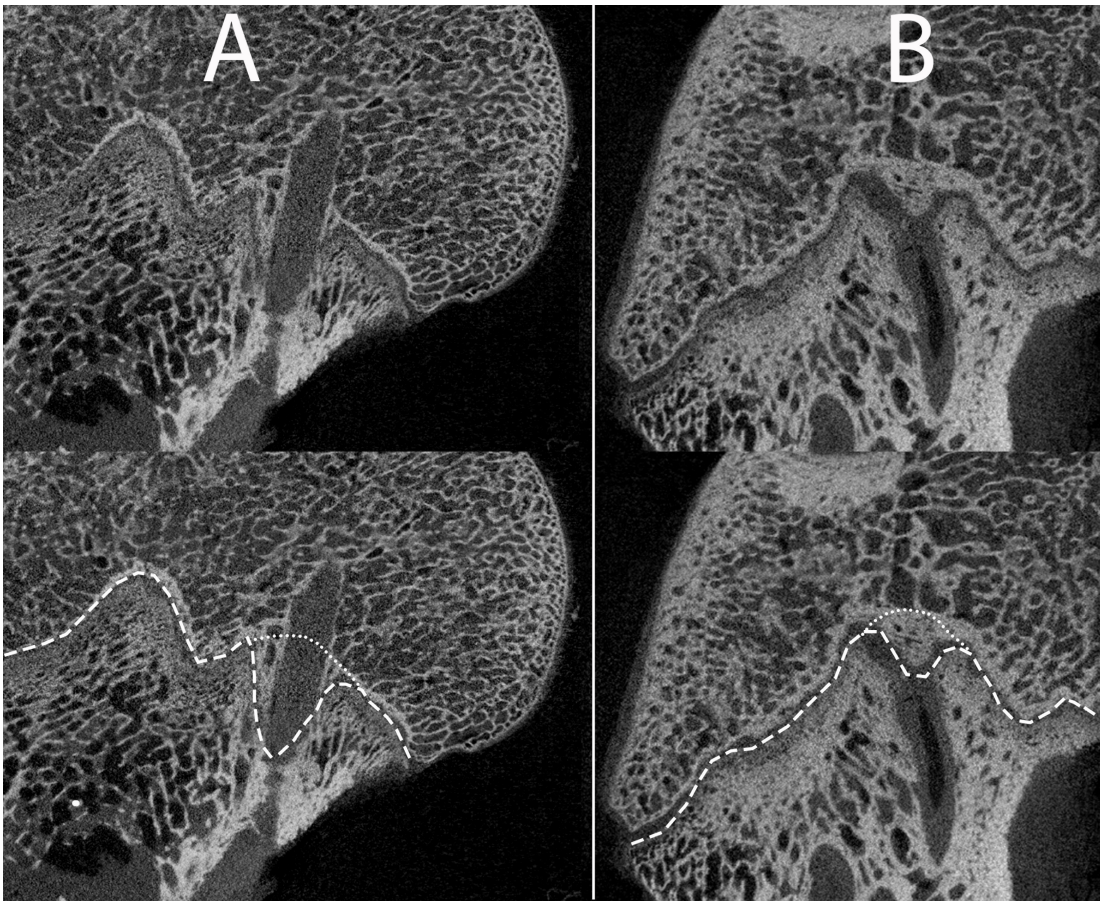

Figure 4.10: Physeal tethering. (A,B) show the two cases of physeal tethering. Dashed line denotes the actual growth plate morphology, dotted line denotes expected morphology.

4.4.4 Micro-CT analysis part 2: Quantitative assessment

10 pairs of distal femora were available for evaluation. From the sagittal micro-CT images, a 3D Region of Interest (ROI) of the growth plate was produced, as were ROIs for the Helical Nails (Figure 4.3, Figure 4.2). This allowed the measurement of:

1. Growth plate disruption
2. Growth plate thickness
3. Bony infiltration of the growth plate

Growth plate disruption

The percentage of growth plate disruption was determined by dividing the nail volume by the physeal volume (NV/PV%). The mean percentage disruption by the Helical Nail was 3.4%, (standard deviation ± 1.1%, median 3.6%, interquartile range 1.1). There was no statistical relationship between percentage disruption, and the presence of bony bridges or physeal tethering (p= 0.36 and 0.56 respectively). Calculation of growth plate disruption by the Kirschner wires was no possible as the areas damaged could not be reliably identified in all samples.

Growth plate thickness

The mean growth plate thickness was calculated for each sample and is shown in Figure 4.11. There was no statistical difference in thickness between the control and Biotrak groups after 6 months of growth (Control mean 0.8mm, ± SD 0.36, Biotrak mean 1.02mm, ± 0.33, p=0.3).

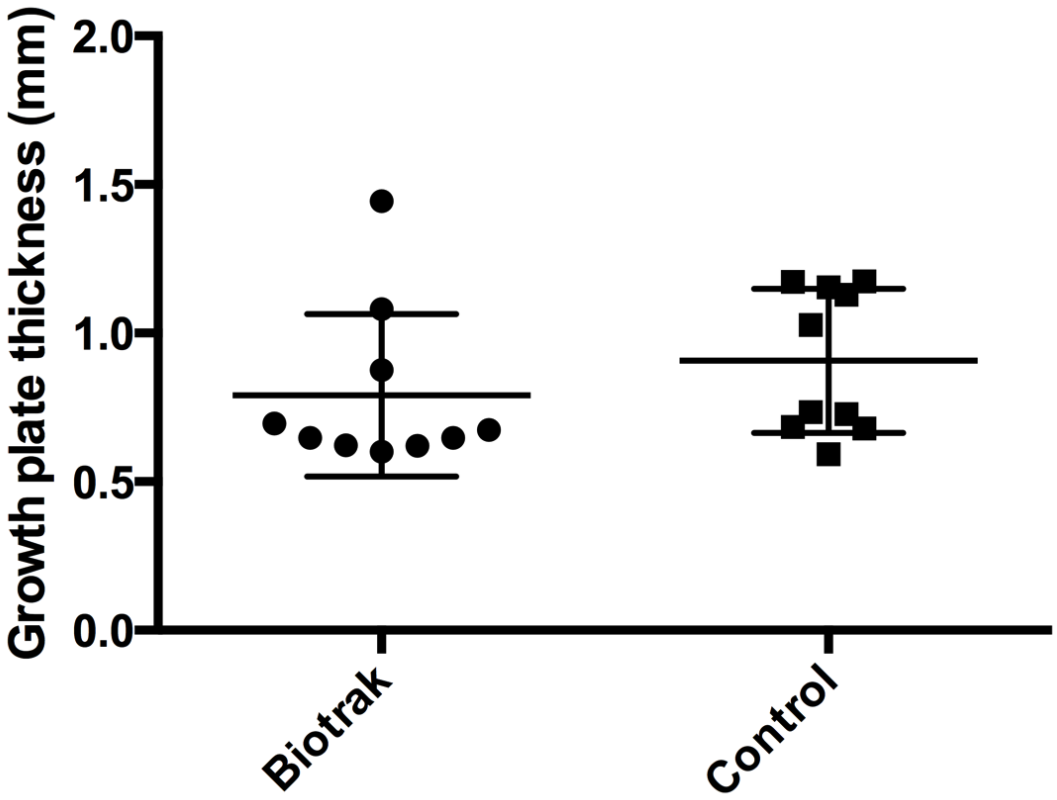

Figure 4.11: Growth plate thickness. Mean and standard deviation displayed.

Bone infiltration of the growth plate

Bone infiltration into the growth plate for the automatic threshold and the manual threshold are shown in Figure 4.12 and Figure 4.13 respectively. The automatic threshold setting produced a consistently higher BVF compared to the manual setting. The program appears to increase the brightness of the binary image, thus increasing the perceived volume of bone within the ROI. Despite the difference in BVF between the threshold settings, comparison of the control and Helical Nail groups BVFs within each setting showed no statistical difference (Manual threshold: control mean BVF 53.5% ± SD 7.7, Biotrak mean BVF 54.0% ± SD 2.8, p = 0.3. Automatic threshold: control mean BVF 91.2% ± SD 18.7, Biotrak mean BVF 82.4%, ± SD 3.6, p = 0.16).

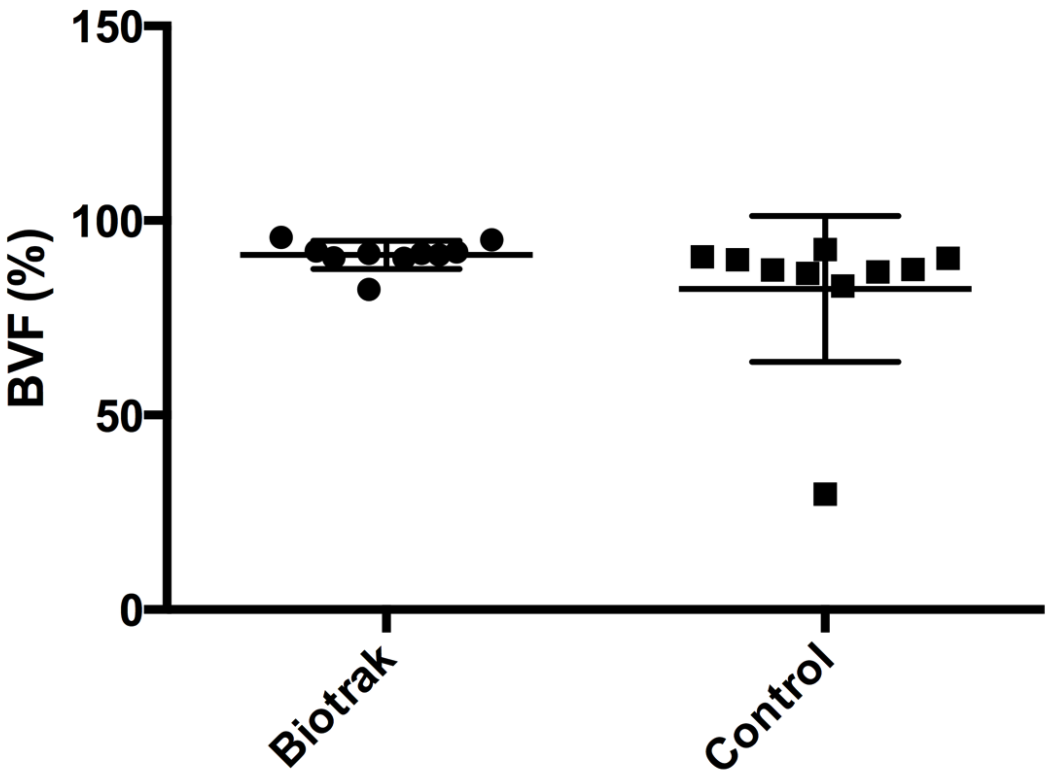

Figure 4.12: Bone infiltration: automatic thresholding. Mean and standard deviations displayed.

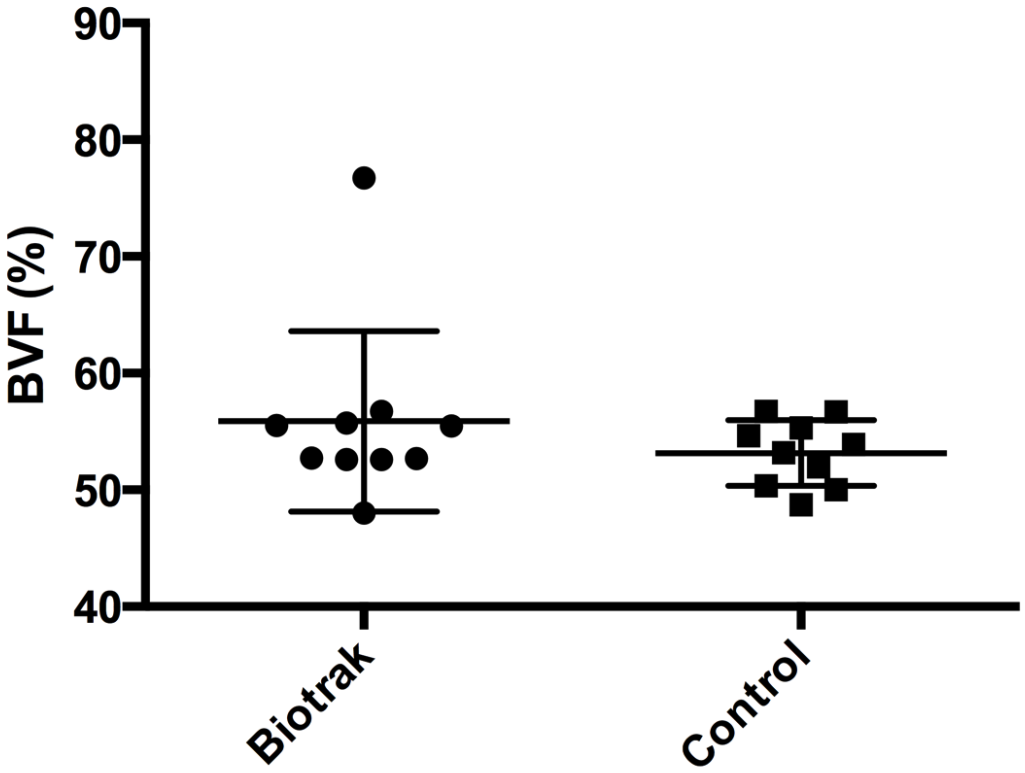

Figure 4.13: Bone infiltration: manual thresholding. Mean and standard deviation displayed.

4.4.5 Histopathological analysis

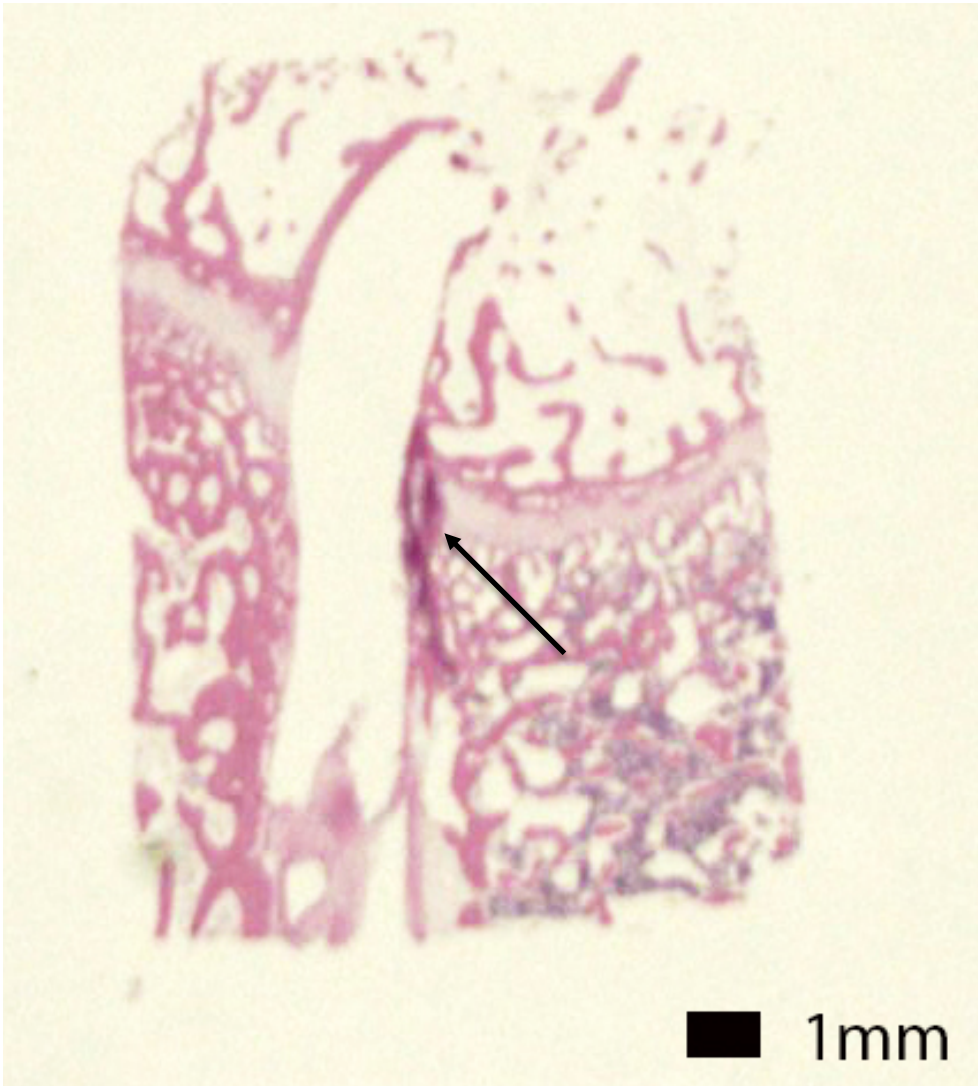

Figure 4.14: Helical Nail traversing the physis. Haematoxylin and eosin stain, black arrow shows a bony bridge adjacent to the pin

Of the two sampling methods (core samples vs sequential cuts), sequential cutting provided significantly superior samples. This method allowed the investigator to ensure a sample contained a portion of the growth plate that had been invaded by a Helical Nail. Of the 21 Helical Nails inserted, 13 had slides that captured the locations where the nail traversed the growth plate. Based on the qualitative micro-CT results, the slides were placed in one of three groups: physeal tethering, bony bridges, or no effect.

Slides from all three groups showed variable amounts of fibrovascular connective tissue lining the tract of the pin. Polarizable material, representing the disrupted pin, was present within or near the pin tract. There were no signs of acute inflammation, nor were there of a foreign body reaction or granulomatous inflammation. Out with the pin tract there was no discernible difference in bone morphology or osteoblast/osteoclast activity between the groups. Although there was drying artefact affecting the marrow, it was structurally normal.

The appearances of the physis remote from the pins was normal with no evidence of physeal death. As predicted from the micro-CT analysis, bone was found to cross the physis immediately adjacent to the pins in the "tether" and "bony-bar" groups. No bone was seen crossing the physis in the "no effect" group.

4.5 DISCUSSION

4.5.1 Helical Nail: practicalities of use and performance

The Helical Nail is a simple device that is implanted after the insertion of a 1.6mm guidewire and passage of a proprietary 2mm reamer. Despite this, difficulties were encountered during insertion with one procedure abandoned entirely. In specimen six a kink in the guidewire blunted the reamer and resulted in inadequate tunnel preparation. There were further issues with minor guide wire kinking which resulted in partial reamer blunting: three reamers were required to insert the 24 Helical Nails. The minor guidewire kinks necessitated increased force to pass the reamer, likely increasing heat generation and thermal damage. This problem was limited, but not eradicated, by careful scrutiny of the intra-operative radiographs to check guidewire integrity. While the availability of intra-operative Image Intensifier radiographs would further improve guide wire insertion in the clinical setting, 1.1mm guide wires are less stiff than those most commonly used in fracture fixation (1.6mm) and remain prone to bending/kinking whilst passing though cortical bone. The thin wires could also be more prone to deformation if required to support a bony reduction during canal preparation.

Inspection of the 11 distal femora showed that all Helical Nails had remained in their original position within the epiphysis, as evidenced by the presence of the nail flare at the insertion site. The crossed Kirschner wires in the control leg were not retained post-surgery so a direct comparison of implant hold was not possible. However, it is well accepted that Kirschner wires typically loosen between 4-8 weeks.

From a surgical perspective, the Helical Nail performance was mixed. It appeared to provide a solid hold within cancellous bone but there was difficulty in the management of the fine gauge guidewires. The importance of a straight guidewire, and the potential requirement for repeated wire passage, could result in unwanted growth plate injury. However, despite an initially steep learning curve, successful implantation with minimal physeal irritation was achieved.

4.5.2 Femoral length after insertion of the Helical Nail

Two measurements were taken to ascertain whether the passage of two Helical Nails caused a growth disturbance. Femoral growth was not significantly different in either assessment, suggesting the nails do not have an adverse effect on femoral growth. The measurement of skeletonised bone and the use of radiographic reference wires are previously documented methods of assessing growth after physeal injury (205, 206). Albeit relatively simple measurements, these are not dissimilar to the current standard in clinical practice, where limb measurement and radiography are the mainstays of length assessment. More accurate measurements can be achieved with micro-CT imaging of the entire bone, but this is confined to smaller animals due to the size of the scanning cabinet(207).

4.5.3 Helical Nail morphology at 6 months

Perhaps the most interesting finding of the qualitative component of the micro-CT analysis was the morphological assessment of the Helical Nails. Scanned six months after insertion, the nails had retained their overall structure (the outline and cannulated centre were easily visible in each scan), but with an alteration in their shape due to intervening growth. The changes appeared to be determined by the nail's trajectory relative to the growth plate. Figure 4.7 demonstrates the proximal and distal portions of the nail remained in their initial positions, parallel to one another. The portion within the physis had become elongated, leaving a track in line with the longitudinal axis of the femur. This was more apparent in nails that crossed the growth plate at an acute angle. Those nails with a trajectory perpendicular to the growth plate were relatively unchanged, albeit lengthened. It can be deduced that the tensile strength of the Helical Nail was overcome by the force of longitudinal growth. It is not possible to state the time point at which the nails lost their integrity. Ideally the Helical Nail would maintain maximal structural influence for four weeks to allow healing, after which it would not hinder growth. However, this study measured growth at a single time point, and conclusions cannot be drawn as to the moment at which the Helical Nails were overcome by growth.

4.5.4 Bony bridges and physeal tethering

An important factor contributing to angular deformity after physeal injury is the formation of bony bridges and physeal tethers. While trauma and infection can cause tethering, iatrogenic insult can also contribute to the problem. The size, location, number of passes, and number of pins all contribute to the physeal injury at the time of surgery. A rabbit model designed by *Dhal et al.* showed that 5 of 60 (8%) transphyseal Kirschner wires that has been in situ for 4 weeks caused a bridge (208). They also identified the phenomena of bony spikes – outpouchings of bone that entered but did not cross the physis – but did not comment on the number or distribution.

This study demonstrates that both Kirschner wire and Helical Nails can cause bony bridge formation. The numbers in both groups were greater than expected, most likely due to the accuracy of the micro-CT assessment. More interesting was the frequency of bridge formation after the single passage of a Kirschner wire, compared to the insertion of a Helical Nail (Kirschner wire: 54% vs Helical Nail: 35%). It could be argued that a freshly injured physis, with a gap left by the temporary intrusion of a wire, allows haematoma infiltration and subsequent bony bridge formation. In contrast, the Helical Nail fills the reamer defect and limits bleeding, theoretically limiting initial bridge formation. A degree of bridge formation whether due to injury, surgery, or a combination of both may be inevitable but questions remain over their relevance. Not all bridges result in physeal tethering or a clinically relevant growth disturbance. Theoretically, a bridge will cause some degree of uneven local growth but there is often sufficient healthy physeal tissue adjacent to the bridge to compensate. In a small retrospective analysis of seven human patients with a centrally located distal femur bony bridge, only one was found to have a clinically significant leg length discrepancy (166). It was concluded that normal hydrostatic growth forces can overcome limited central bridging to allow continued, essentially normal, longitudinal growth. This is complimented by animal studies that demonstrate the formation of bridges but no significant growth discrepancies(170, 208, 209). Therefore, focus should not only fall on the presence of bony bridges and tethers, but at which point they being to influence growth so to cause clinical

deformity. In this study, two specimens had a physeal tether that caused a change in the expected growth plate morphology. By examining the CT images adjacent to the tether, interruption of the normal growth plate shape could be identified. Despite the presence of tethering however, and within the limitation of this study, no significant difference was found in the limb length. Thus, the question of bony bridges, physeal tethers and at which point they influence limb development remains unclear.

4.5.5 Micro-CT quantitative analysis of the growth plate

Micro-CT as a replacement for histomorphometry

Quantitative analysis of the bony samples has previously relied upon the techniques of histomorphometry. More recently micro-CT has been offered as an alternative. Performed at extremely high resolution, it allows assessment of an entire region, without the need for estimation or the destructive processes required to produce microscopy slides. This method was first developed to assess cancellous bone taken form the human spine, femur, iliac crest and calcaneus (210). Numerous established histomorphometry measurements such as bone volume and surface density were more accurate than traditional methods, while micro-CT also offered information relating to trabecular thickness, separation and number. This technique was then used to characterise a rat growth plate. Martin *et al.* assessed the microarchitecture of the proximal tibia in the rats of varying age and demonstrated the sequence of physeal closure(211). They showed that as rats mature, the growth plate thins with an accumulation of microscopic bone struts and mineralisation. A model of growth plate disruption and subsequent micro-CT quantification was subsequently developed by Coleman *et al(207)*. A 2mm drill was used to create a longitudinal defect in the distal femur with measurement of bone infiltration to the defect and growth plate thickness. This was complemented by other works that have used a similar model to define growth plate injury (212). In the present study, micro-CT was used for the first time to quantify the percentage physeal disruption, physeal thickness and bony infiltration in an ovine model, to evaluate growth plate health after iatrogenic injury.

Growth plate disruption

Implant diameter represents an important difference between the Kirschner wires (1.6mm) and Helical Nails (2.5mm). 1.6mm wires are common in upper limb fracture management and have a cross sectional area of 2.01mm^2. The Helical Nail on the other hand, has a diameter greater than even the 2mm wires commonly employed in the lower limb, with an area more than double that of 1.6mm wires at 4.91mm^2. For many clinicians, the use of the Helical Nail would present concerns regarding increased growth plate disruption. Contention remains over the amount of growth plate damage that leads to local physeal arrest. Rabbit models by Janarv *et al.* and Makela *et al.* first attempted to define the percentage cross sectional disruption that would lead to growth disturbance. They suggested that a penetrating iatrogenic injury compromising 7-9% of the growth plate caused disturbance, while no change was seen in injuries of 4-5% (169, 171). Further work in rats confirmed that large defects of 11% caused a leg length discrepancy (213). A study of femoral and tibial growth in sheep after physeal injury of approximately 15% showed significant alteration in femoral length and morphology (214).

In this study, growth plate disruption by two Helical Nail was 3.4%, which did not affect femoral growth. No relationship was found between the percentage disruption and the presence of bony bridges or physeal tethers. While this volume of damage was below the threshold required to cause physeal dysfunction, it cannot be directly translated to the human setting. The growth plate of the human elbow or distal radius is smaller than that of the ovine distal femur, and it is likely that a Helical Nail would cause a larger physeal injury. As an estimation, anteroposterior elbow radiographs of children at various ages were measured to provide an average distal humerus width, and allow a calculation of physeal disruption based on the combined width of two helical nails (5mm). Percentage disruption was 16%, 13%, 12% and 10% for two, four, six and eight year olds respectively. These figures are higher than in the ovine model, and approach the upper threshold of acceptable physeal damage.

Growth plate thickness and bone infiltration

The normal growth plate becomes thinner with age, as small bony bridges or tethers between the metaphysis and epiphysis proliferate and increase mineralisation. These changes forecast the physiological closure that defines skeletal maturity. It has been previously demonstrated that a sufficiently large physeal defect will result in a premature decrease in physeal thickness with a complimentary increase in bony infiltration (207, 211). It is therefore inferred that thickness and bony infiltration provide insight into the overall health of the immature growth plate. There was no statistically significant difference between the Helical Nail and Kirschner wire groups in either of these measurements. This adds to the previous evidence that the damage to the growth plate is similar for both groups.

The measurement of bone infiltration brought to light an interesting idiosyncrasy of the micro-CT analysis. The program creates a binary image of each CT slice by thresholding the greyscale original (i.e. dividing it into pixels that are deemed "bone" or "not bone"). Morphometry of the binary images then provides a value for the amount of bone within a region. The key to this process is thresholding – defining what tone on a grey scale constitutes bone rather than cartilage, marrow or dead space. The program offers an automatic calculation but inspection of images demonstrates that it potentially over estimates bony material. Manual thresholding was therefore performed to compliment the automatic settings. This was achieved by studying the intensity histogram of the greyscale image, and selecting a threshold value that best represents bone. This resulted in lower BVF values compared to the automatic setting but did not result in a significant difference between the two test groups. This suggests that the automatic threshold function may not be entirely accurate and future work should include a manual selection.

4.5.6 Histopathology

Although sampling was somewhat limited, the histopathological analysis served to confirm aspects of the Micro-CT assessment. The bony formation evident on the scans was present on numerous slides, but importantly the surrounding physis had a

normal appearance (Figure 4.14). The remaining healthy physis can therefore continue to grow and overcome small bony bridges, limiting the effects of the implant. Perhaps more importantly, there was no evidence of an acute inflammatory or foreign body reaction, despite the implant loosing structural integrity. Absorbable polymer implants have previously been associated with osteolytic reactions and the formation of sterile sinus', particularly in rapidly degrading variations. The absence of this phenomena in the Helical Nail group is most likely explained by slow dissolution rate PLLA, which limits the rapid accumulation of degradation debris. These findings suggest that, within the limits of this study, the Helical Nail is a benign device. However, the study period was not sufficient to exclude the risk of subsequent adverse soft tissue reactions, which can occur up to 5 years after insertion (Section1.5) (138).

4.5.7 Limitations of the model

Ovine model

The majority of studies have focused on rat and rabbit models(169, 171, 207, 208, 212). Sheep were selected in this study to assess the effect of the Helical Nail on a large animal growth plate, to provide a more realistic representation of the human response. Timing of surgery becomes more important when using larger animals as offspring are produced seasonally rather than year-round. In this study surgery was delayed due to an unforeseen problem in the processing of an animal testing license amendment. As a consequence, the sheep underwent surgery at 6-7 months, rather than the proposed 4-5 months. There were concerns that this could adversely limit the amount of remaining growth, leading to an underestimation of any effects of the Helical Nail. Evidence on sheep growth and timing of physeal closure is limited. A large study of Shetland breed sheep suggested that the distal femur physeal fusion occurs around 40 weeks(215). However, the Shetland is a small, unimproved sheep used for wool production and does not fully represent the much larger sheep in this study that are typically used for meat. The concerns over remaining growth were allayed by the plain radiographic and Micro-CT assessments that not only

demonstrated significant growth post-procedure, but also the presence of an open physis at the time of euthanasia.

The method employed for the control limbs deviated from current clinical practice. Financial and licensing restrictions meant a second procedure to remove wires three weeks after their insertion could not be performed. Therefore, the wires were inserted and immediately removed in an attempt to simulate the physeal damage typical of the human procedure. However, it is unclear whether a wire left *in situ* for 4 weeks, or one that is immediately removed, results in greater bony growth across the physis. Previous works into bony bridge resection surgery have raised concern that a residual unfilled defect may promote recurrence, as fresh haematoma infiltration can lead to bony bridge formation. Interposition of an inert compound (autologous fats, tendon, bone cement or agarose gels) has been shown to inhibit infiltration of trabecular bone into a newly formed defect (167, 169, 207, 216). In this study, the specimens in the Kirschner wire group were more prone to bony bridge formation (without an increase in overall bony infiltration) than the Helical Nail group. This could be explained in two ways: that the creation of an empty defect increases bridge formation, or the interposition of a Helical Nail limits it. Therefore, there is potential for the control to overestimate the bony infiltration that would be expected in the clinical setting. This could lead to the falsely reassuring assertion that the Helical Nail causes a lesser insult than Kirschner wires, due to the comparable percentage of bone infiltration and fewer bony bars. The use of an uninjured control would have offered a fuller assessment of any growth disturbance caused by the helical hail, eliminating the problems described.

Animal models of physeal damage and resultant growth typically involve drilling of an uninjured physis (167). This method allows assessment of the effects of surgery that necessitates invasion of a healthy physis to achieve fixation, such as supracondylar elbow fractures. It does not offer insight into the outcome of different fixation methods of a traumatically injured physis, such as Salter-Harris injuries of the distal radius. The effects of the insertion of a transphyseal bioabsorbable implant to an injured physis cannot be directly extrapolated from this experimental model. To achieve this, a reproducible growth plate fracture model would be required,

something that has not been well established in the literature. As such, no assertions can be made regarding the effects of the Helical Nail in stabilisation of traumatic growth plate injuries.

Measurement of femoral growth and morphology

While Micro-CT assessment provided accurate information relating to the distal femur physis, criticism could be directed towards the lack of an initial assessment of length. Accurate measurement of femoral length before Helical Nail insertion could have been desirable but was not undertaken for two reasons; gross measurement of the bone through soft tissue was unreliable, and the use of standardised full length plain radiographs was not possible. Full femur radiography has been used in previous works but inaccuracies in positioning and variation in radiographic magnification are described (214). Instead, measurement of a skeletonised femur was used to compliment the radiographic assessment of growth that used the *in situ* transverse Kirschner wire.

Assessment for the development of any distal femur deformity was lacking. The distal femur physis is a complex structure that is commonly implicated in growth abnormalities after injury (11, 217). The deformity can be multi-planar and is therefore incompletely appreciated on plain radiographs of the knee. Certainty that a new device does not cause a growth aberration relies on the identification of subtle changes of angulation or rotation in any plane. This could have been achieved using one of two methods. Plain CT scanning before insertion and at six months, would have provided a 3D model to allow comparison and identification of any abnormality. Perhaps more useful would have been the employment of radiostereometric analysis. The implantation of multiple small radio-opaque beads at defined positions, with subsequent synchronous plain radiographs, would have provided 3D assessment of a developing deformity. These could have been undertaken in a serial fashion, with minimal disturbance to the animal, to allow real time assessment of growth and the development of any abnormality.

Histopathological assessment

A limited number of samples that contained both the Helical Nail and an appropriate cuff of surrounding physeal tissue were available for analysis. The large nature of the specimens necessitated significant resection to provide samples suitable for decalcification and staining. Within the control group it was not possible to macroscopically isolate bony bars for slide preparation. Refinement of the resection technique in the Helical Nail group provided a number of appropriate samples with sufficient physeal tissue adjacent to the Helical Nail. There is no recognised classification or grading system for the effect of an absorbable implant on the physis to provide a quantitative analysis. As such, only a descriptive analysis was undertaken to complement the Micro-CT assessment.

4.5.8 Conclusion

The Helical Nail, its surgical implantation, and influence on femoral growth and the distal physis, were assessed and compared to traditional Kirschner wires. The device is relatively simple but issues in canal preparation were encountered on several occasions. The assessment of femoral growth did not show any significant difference between the two groups six months after surgery. Micro-CT and histological analysis showed minor variation in bony bridge and physeal tether formation but no quantitative differences in the physis. There was clear evidence that the tensile strength of the Helical Nail was overcome by subsequent growth, a desirable quality in an implant of this nature.

Section 5: Discussion

5.1 THE KEY QUESTIONS

This study aimed to identify issues with the current practice of Kirschner wire stabilisation of paediatric supracondylar fractures of the elbow, and to define the suitability of an alternative, bioabsorbable implant. Three key questions were asked (section 1.8):

5.1.1 What is the complication rate of Kirschner wire fixation in the local population, and does this warrant the introduction of a new surgical method?

Infection, malunion and nerve injury are the most common complications after supracondylar elbow fracture fixation in children. An overall infection rate of 9.6% was found over the course of the 2.5 year period, with a major infection rate of 1.3%. The minor infection rate was slightly higher than other large studies, however, this is due to variations in the definition and reporting of minor infection, rather than inappropriate surgical practice(13, 15). A single case of iatrogenic ulnar nerve injury occurred during the placement of a medially based wire. No cases of malunion required corrective surgery.

This arm of the study identifies infection as the main issue in Kirschner wire fixation of supracondylar elbow fractures. The lack of significant malunion suggests that the surgical construct achieved with Kirschner wires is adequate. A bioabsorbable implant that can demonstrate comparable mechanical characteristics, would allow primary skin closure at the time of surgery and potentially lower infection rates, without compromising construct stability. The elimination of secondary removal procedures (3.6% of patients) would be an additional benefit. Investigation into the Helical Nail was warranted due to its potential benefits in paediatric fracture surgery.

5.1.2 Is the Helical Nail mechanically comparable to Kirschner wires?

Helical nail strength was comparable to crossed Kirschner wires in resisting rotational force but inferior in extension. Rotational deformity has been cited as a key component in cubitus varus, as the resultant loss of cortical apposition leads to development of the deformity. Extension is a less commonly cited factor in malunion of supracondylar fractures, but remains a significant component of the initial injury. The outcome of the rotational testing was encouraging but the inferiority in extension testing leaves doubts over the suitability of the implant. Given the current design, the Helical Nail demonstrates insufficient strength to warrant use in the fixation of supracondylar elbow fractures.

5.1.3 Does the Helical Nail affect the growth plate, and if so, does this result in limb length discrepancy?

For the first time in a large animal study, Micro-CT was used assess physeal injury. Average physeal disruption by two helical nails was 3.4%, a figure below the described threshold of 7-15% that is reported to result in growth anomalies. The insertion of two Helical Nails did not limit femoral growth. Quantitative assessment of the Micro-CT scans allowed visualisation of physeal morphology. Bony bridges were seen in both groups, with a slight preponderance in the control group. True physeal tethering, where a bony bridge resulted in a change of growth plate morphology, was only seen adjacent to two Helical Nails. However, in the absence of any abnormality in femoral growth or length, the importance of this finding is unclear. This uncertainly is reflected in other works, encompassing both rat and human models, that have demonstrated physeal tethers but no discernible change in femoral length or angulation(207, 208, 212).

The quantitative Micro-CT analysis served to provide surrogate markers of physeal health. There was no difference in the volume of bony infiltration of the physis or physeal thickness between the two groups. This was complemented by the histopathological analysis which showed normal appearances of the physis and no

evidence of a foreign body reaction. These results suggest that the Helical Nail did not have an adverse effect on the growth plate.

Beyond the assessment of the physis and femoral length, one of the most striking findings revealed the influence of growth on the Helical Nails. Each implant remained anchored in the epiphysis and metaphysis, but the portion that had resided within the physis had become elongated in line with the axis of growth. Growth plate hydrostatic forces had overcome the tensile strength of the helical nail which serves as a significant indicator that the Helical Nail did not hinder growth.

5.2 CONCLUSIONS

The hypothesis in section 1.9 has not been unequivocally confirmed.

The helical nail displayed numerous desirable characteristics including:

- Strong resistance to rotational deformity in a supracondylar fracture mode
- No surgical infections or complications
- No leg length discrepancy at six months
- An acceptable volume of growth plate destruction (3.4%)
- No greater formation of bony bridges or physeal mineralisation compared to the control
- No thinning of the growth plate compared to the control
- Inert histopathological appearance with no evidence of a foreign body reaction

Less desirable characteristics were also identified:

- Short length necessitates the use of a medially based implant
- Poorer resistance to an extension force
- Difficulties with insertion may lead to unnecessary physeal injury

From this data, the current Helical Nail does not demonstrate sufficient mechanical strength for immediate use in humans. The results of the Micro-CT and histopathological evaluation are encouraging particularly in the context of the unhindered femoral growth. Despite this, the presence of physeal tethers and the lack of 3D multi-planar imaging to exclude the presence of deformity, casts doubt on the Helical Nails suitability.

5.3 FUTURE WORK

This study offers numerous avenues for work to provide additional evidence to support the use of the Helical Nail in paediatric trauma surgery. These include improvements in implant design, methodology and a pilot study.

Development of the implant

Biomechanically, the Helical Nails limited length inhibited its ability to secure the simulated fracture. The nail configuration deviated from the clinical norm, by relying on a columnar hold, with only a single cortex engaged with each implant. A clear area for improvement would be the development of longer nails. This would increase the working length and allow for a "lateral' configuration with the engagement of two cortices per nail. These changes could potentially improve the biomechanical properties of the surgical construct to resist both rotation and extension. The modification of the implant diameter may also be of interest. The Helical Nail is 2.5mm, 0.5mm wider than the commonest width of Kirschner wire in common use. Some clinician may object to this increase in size due to the greater volume of growth plate disruption. If the implant were longer, and could therefore achieve a bi-cortical hold, a narrower diameter Helical Nail may be well tolerated and provide adequate stability.

Identifying growth disturbance

Future studies that assess the effect of an implant on a large animal physis should consider the use of 3D assessment of femoral length and morphology. The lack of any growth disturbance is the most important outcome of this study, but its impact could have been heightened by the addition of CT analysis of the femur. Not only would this have this provided a second, repeatable, means of length assessment, it would have allowed the identification of any subtle deformity resulting from a physeal tether. Multiple scans at predetermined times would also identify the point at which the Helical Nail was overcome by longitudinal growth.

Potential in other physeal injuries

This study focussed on the potential of the Helical Nail for use in peri-physeal fractures that affect the supracondylar region of the humerus. The adjacent physis has a complex shape and is slow growing which potentially increases the risk of growth disturbance. The Helical Nail may have potential for use in the distal radius which has a more linear physis that is rapidly growing. It is conceivable that this physis would have greater capacity of overcome any tethering effects of the Helical nail.

Human pilot study

The use of the Helical Nail in humans is currently precluded by their short length. If this was to be addressed, the current evidence would suggest that they do not hinder growth and could be applied to humans. Drawing from the evidence presented here, their use may be more suitable in fractures of the distal radius.

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Appendix 1: Permission to Access Patient Records

PROJECT PROPOSAL AND REGISTRATION FORM

Please see sections in the workbook for guidance on completion of the form.

Please note - your form will be returned if any section is blank.

Project Title: *Post complications rates of Paediatric fractures fixed with Kirschner wires*

Why was the project selected?

Paediatric orthopaedics department wish to know the rates of infections from this particular procedure to compare it to values available in the literature (comparison to a figure of 8% infection)

Objective(s): *(Why are you doing the project and what do you hope to achieve – see section E)*

I hope to show that the department has an infection rate no more than is commonly quoted to ensure the standard of care is appropriate

Appropriate Quality Improvement Team Children's services

Main project contact:

Name	Sam Mackenzie
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Methodology *(brief outline) (see section F)*

Patients who have had a Kirschner wire inserted for the reason of fracture fixation (over the last 3 years) will be identified from the RHSC theatre X-ray log book. CHI numbers will be identified and stored on an excel sheet only kept on an NHS computer. The TRAK records of the patients will then be scrutinised to assess demographics of injury, injury type, history and whether there were any complications or infections. This information will be held on an excel sheet separate from the CHI numbers – with a new unique patient code used for this project used to identify the patients. The information will be discussed with the local service.

Estimated start date:		**Estimated completion date:**	
(day /month /year):	26/3/15	*(day /month /year):*	26/6/15

Confirmation that the governance topics in this workbook have been addressed (✓):	**Brief explanation if the governance topic is considered to be not applicable**
☒ Other people involved (Section H)	A medical student will assist in the interrogation of TRAK. Alex Wallace.
☒Literature search (Section J)	
☒Resources (Section K)	
☒Ethical considerations (Section L)	
☒ Equality and Diversity (Section M)	
☒Consent (Section N)	
☒Data protection (Section O)	
☒Caldicott principles (Section P)	